August 8, 2001

Mr. Anthony Britten
Special Review and Reregistration Division
Office of Pesticide Programs (7508C)
U.S. Environmental Protection Agency
Room 266A, Crystal Mall 2
1921 Jefferson Davis Highway
Arlington, Virginia 22202

Corr. # daL075-01

Dear Mr. Britten,

Re: **Carbaryl; Chemical number 56801; EPA Reg. No. 264-324**
Review of the Preliminary Risk Assessments for Human Health and for Environmental Fate and Ecological Effects for the Reregistration Eligibility Decision on Carbaryl

We have completed our review of the preliminary human health and environmental fate and ecological effects risk assessments for the Reregistration Eligibility Decision of carbaryl. Our comments on the Agency's assessments are enclosed in the following documents:

- Review of the Draft Human Health Risk Assessment
- Review of the Draft Environmental Fate and Ecological Risk Assessment for the Reregistration of Carbaryl

Hard copies of the above documents will be sent by express mail within the next week.

Key issues discussed in these documents are as follow:

DRAFT HUMAN HEALTH RISK ASSESSMENT

FQPA Considerations

A 2-Generation reproduction study was recently completed and submitted to the Agency. The No Observable Effect Levels (NOELs) for carbaryl administered in the diet, in CD® (SD) rats under the conditions of this study, were:

- For parental systemic toxicity: 75 ppm
- For parental reproductive toxicity: 1500 ppm
- For offspring toxicity: 75 ppm

In addition, Aventis has submitted to the EPA a revised Developmental Neurotoxicity Study (DNT) which demonstrated that no alterations in brain morphometric measurements were observed in the offspring, thus no increased sensitivity was observed in the pups.

Aventis firmly believes that with the submission of these two studies, the data gap for the 2-generation reproduction study is fulfilled and the issue with the developmental neurotoxicity study is resolved. Thus, the Agency has the required data to justify removing the extra 10X FQPA Safety Factor from the risk calculations throughout the Human Health Risk Assessment for carbaryl.

Additional Uncertainty Factors

For the chronic study in dogs, Aventis does not agree with the additional 3X for a lack of a NOEL in the study. According to the policy issued in August 2000 concerning the endpoint for selection for cholinesterase inhibiting compounds, the Agency stated that the red blood cell (RBC) inhibition should be used instead of the plasma. The NOEL for RBC cholinesterase inhibition was 125 ppm (3.1 mg/kg/day). Additionally, Aventis believes that the brain cholinesterase inhibition observed at the 125 ppm level was slightly above background level and was not of toxicological concerns due to the lack of clinical signs observed at this dose level. Furthermore, Aventis performed a five-week study in dogs, which agreed with the results of the chronic study. Therefore, it is our opinion that all calculations based on the chronic dog in the document should be adjusted to reflect the removal of the 3X-safety factor.

Cancellation of Certain Uses of Carbaryl

Use on Barley, Oats, Rye, and Cotton: Changes should be made throughout the Human Health Risk Assessment and associated supporting documents to reflect the cancellation of the use on barley, oats, rye, and cotton. It should be noted that Aventis CropScience labels for the technical materials and the end-use products containing carbaryl were amended to delete these uses. The Agency has already approved the labeling changes.

Use on Poultry: Aventis CropScience will no longer support the use of carbaryl for direct application to poultry, as well as the poultry quarters treatment. We will submit a request for cancellation of these uses in accordance with section 6(f)(1) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). The cancellation of this use causes a significant improvement in the risk assessment since poultry are the major contributor to the risk estimate. We believe that only the dietary analyses conducted without poultry should be included in the HED Chapter. Analyses including poultry would be unrealistic and misleading.

Dietary Exposure Assessment

An industry-sponsored Carbamate Market Basket Survey (CMBS) was conducted and submitted to the Agency for use in the dietary exposure and risk assessment for carbaryl. The Carbamate Market Basket Survey Task Force met with EPA/HED before the start of the study to review the purpose and design of the study. The EPA assured the task force that the study data would be used in risk assessments, taking precedence over all other monitoring or field trial data available for those crops. A surrogation plan according to HED SOP 99.3 was also assured. These data provide more realistic measures of residues to which consumers are exposed and they should be included in the dietary analyses as agreed upon by the CMBS Task Force and the EPA.

Water Exposure Assessment

EPA has based its assumptions about concentrations of carbaryl in drinking water upon model simulations. Aventis CropScience conducted a drinking water monitoring program that provides the best estimate of concentrations of carbaryl in drinking water. The study uses the sampling design for acute endpoints recommended in industry/EPA meetings during 1999 (weekly sampling during times of peak concentrations over a three-year period). Twenty sites, representative of the most vulnerable community water systems in the highest use areas of carbaryl, were selected. These included 16 sites in agricultural areas and 4 locations in urban areas. Samples were collected from the inlet and outlet water at each sampling interval. Outlet samples were only analyzed when residues were present in the inlet samples. The analytical method has a limit of quantification of 0.030 ppb and a limit of detection of 0.002 ppb.

The study provides information on concentrations of carbaryl in community water systems most likely to contain the highest concentrations of carbaryl. Residues of carbaryl in other areas would be expected to be

lower. The study should be used in the carbaryl exposure calculations as it provides the drinking water concentrations needed for FQPA dietary assessments.

Occupational and Residential Exposure Assessment

Aventis CropScience has conducted, or is in the process of conducting, studies relevant to the refinement of the occupational and residential risk assessment. These studies are as follows:

Study	**Anticipated Completion Date**
▪ 4-Week Repeated-Dose Dermal Toxicity Study with SEVIN® XLR Plus in Rats.	September 2001
▪ 4-Week Repeated-Dose Dermal Toxicity Study with SEVIN® 80S in Rats.	September 2001
▪ 4-Week Repeated-Dose Dermal Toxicity Study with Carbaryl Technical in Rats.	September 2001
▪ Measurement of Pesticide Exposure of Suburban Residents Associated with the Residential Use of Carbaryl.	March 2002
▪ Biological monitoring of citrus orchard application and post-application apple thinning and cherry harvesting job functions	March 2002

DRAFT ENVIRONMENTAL FATE AND ECOLOGICAL RISK ASSESSMENT

Carbaryl Studies to Fulfill Requirements

Aventis CropScience is in the process of conducting, or has scheduled, studies relevant to the refinement of the environmental risk assessments for carbaryl and the major degradate 1-naphthol. These studies are as follows:

- Rate and Route of Aerobic Degradation in Soils. These studies have been initiated with parent carbaryl applied to four diverse U.S. soils. The data are intended to provide additional half-life determinations for parent carbaryl and the major degradate 1-naphthol.
  Expected completion date: March 2002

- Aerobic Aquatic Metabolism in Two Water/Sediment Systems. These studies have been initiated with parent carbaryl applied to two distinct U.S. water/sediment systems. The data are intended to provide additional half-life determinations for parent carbaryl and the major degradate 1-naphthol. In addition, further identification of additional degradation products is anticipated.
  Expected completion date: March 2002

- Adsorption and Desorption of 1-Napthol to five soils. This study has been scheduled to evaluate the adsorption and desorption of the major carbaryl degradate to five soils/sediment. The data are intended to provide information necessary to evaluate the environmental risks from 1-naphthol in standard models.
  Expected completion date: March 2002

For the reregistration process in the EU, Aventis CropScience is in the process of conducting, or has scheduled, studies relevant to the refinement of the ecotoxicological risk assessments for carbaryl and the major degradate 1-naphthol. These studies are as follows:

- Studies with Carbaryl:

  Acute oral LD50 in mallard ducks
  Dynamic acute LC50 in bluegill sunfish
  Acute toxicity in *Daphnia*
  Acute toxicity in *Chironomus riparius*
  Toxicity in *Selenastrum capricornutum*
  Acute oral and contact toxicity in honeybees
  14-d toxicity in earthworms
  Effects on soil microorganisms (nitrification/carbon cycle)
  Effect on sewage treatment

- Studies with 1-naphthol

  Early life-stage study in fathead minnows
  Acute toxicity in *Daphnia*
  Acute toxicity in *Daphnia* in presence of sediment
  Chronic toxicity in *Daphnia*
  14-d toxicity in earthworms

- Formulated Product

  Vegetative Vigor
  Toxicity in *Selenastrum capricornutum*
  Acute oral and contact toxicity in honeybees
  Effect on non-target arthropods
  14-d toxicity in earthworms
  Effects on soil microorganisms (nitrification/carbon cycle)

<u>Ecotoxicological Risk Assessments</u>

Aventis has pointed out several errors in the PRZM input parameters (see comments made to Tables 5 and 6 of the draft RED). Overly conservative estimates of foliar dissipation half-lives and changes in ecotoxicology study endpoints would dictate a re-calculation of the EECs and risk quotients is warranted in a number of instances.

Endocrine Disruption

Reports in the open literature on the reproductive effects of carbaryl in wild mammals are at best ambivalent. The recently submitted 2-generation study in rats demonstrates the absence of reproductive effects. As EPA pointed out, findings reported in the literature were made at concentrations well above the highest peak concentration modeled. Therefore these findings are irrelevant for a risk assessment and at the current stage of discussion about endocrine disruption. If the concern about the endocrine potential of carbaryl persists, the issue should be revisited once the Agency's endocrine disrupter screening and testing program as well as a policy on how to incorporate positive findings into an ecological risk assessment have been fully developed.

Mobility

The classification of carbaryl as mobile to very mobile is inconsistent with measured K_{oc} values of 177 to 249 (MRID 43259301). According to the widely used classification scheme of McCall, *et al.* (1980) wherein K_{oc} values between 150 and 500 denote medium mobility in soil, carbaryl would be classified as having medium mobility in most soils. This classification of medium mobility is further supported by the acceptable column leaching study (MRID 43320701) in which aged carbaryl residues were only slightly mobile in a number of soils. The mobility of carbaryl would be expected to be higher in sandy soils or in soils of low organic matter.

1-Napthol Fate and Transport

The Agency is requiring additional information on the persistence and mobility of 1-naphthol, a major environmental degradate of carbaryl. However, a half-life for 1-naphthol of less than 1 day can be calculated from the carbaryl aerobic soil metabolism study (MRID 42785101). The data from this study demonstrate that under aerobic soil conditions the formation and decline of 1-naphthol, starting from parent carbaryl, is complete in less than 14 days. This half-life can be used for preliminary environmental fate modeling to estimate EECs for 1-naphthol.

The EPA suggested that 1-naphthol is not strongly sorbed to soil. Additional information available in the literature demonstrates that the sorption of 1-naphthol to soil is stronger than that seen for carbaryl itself. Hassett *et al.* (1981) has demonstrated that the sorption of 1-naphthol was the result of sorption to organic carbon resulting in K_{oc} values between 431 and 15,618. These data indicate that 1-naphthol is less mobile and less susceptible to leaching than carbaryl itself, and they demonstrate that at least a portion of the 1-naphthol residue is tightly sorbed to soil constituents. To meet the requirement for information on the adsorption and desorption of 1-naphthol by the Agency, the registrant is conducting an adsorption/desorption study to meet the 163-1 guideline. Study results should be available for submission to the Agency in the first quarter of the calendar year 2002.

Ground Water

EPA summarized information on the detection of carbaryl in groundwater from the EPA Pesticides in Groundwater Database, the EPA STORET database and the NAWQA database. Each of the databases shows a pattern of very low levels of carbaryl detection in few groundwater resources. These analyses confirm several statements made by the Agency that carbaryl have limited potential to impact groundwater resources. However, on page 2 of the Memorandum issued June 28, 2001, in conjunction with the EFED RED chapter for carbaryl, EPA is requiring additional information on "Surface and groundwater monitoring in urban and suburban use areas (non-guideline)." Based on the characteristics of carbaryl and the available data demonstrating limited impact of carbaryl on ground water resources, additional studies to evaluate the potential for carbaryl to contaminate groundwater are unnecessary and unwarranted.

Please let me know if you need any additional information. My phone number is (919) 549-2718.

Sincerely,

Danielle A. Larochelle

Danielle A. Larochelle
Registration Manager

CARBARYL

Chemical ID No. 056801; Case 0080

Review of the Draft Human Health Risk Assessment

August 8, 2001

Aventis CropScience
P.O. Box 12014, 2 T.W. Alexander Drive
Research Triangle Park, NC 27709

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General Comments

FQPA Considerations

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Aventis CropScience will no longer support the use of carbaryl for direct application to poultry, as well as the poultry quarters treatment. We will submit a request for cancellation of these uses in accordance with section 6(f)(1) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). The cancellation of this use causes a significant improvement in the risk assessment since poultry are the major contributor to the risk estimate. We believe that only the dietary analyses conducted without poultry should be included in the HED Chapter. Analyses including poultry would be unrealistic and misleading.

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Aventis CropScience has conducted, or is in the process of conducting, studies relevant to the refinement of the occupational and residential risk assessment. These studies are as follows:

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Part I - Toxicology Data Base

Line-by-Line Review of the Toxicology Data Base Evaluation from the Human Health Risk Assessment Document for Carbaryl (June 19, 2001)

1.0 Executive Summary

Section Number 1.0

Page: 3 Paragraph: 4 Line: 3

EPA comment:

In the developmental neurotoxicity study in the rat, alterations in brain morphometric measurements were observed in offspring.

Aventis' response:

Aventis has submitted to EPA a revised DNT, which demonstrated no alterations in brain morphometric measurements taken in the offspring, thus no increased sensitivity was observed in the pups. The details of this study will be discussed below in the supporting 'Discussion Section'.

Page: 3 Paragraph: 5 Line: 3

EPA comment:

No acceptable two-generation reproduction study is available.

Aventis' response:

Aventis has submitted to EPA a new 2-Generation Reproduction Study with carbaryl, which neither demonstrated that carbaryl is a reproductive toxicant nor demonstrated that the pups were more sensitive than the dams. The NOELs for carbaryl administered in the diet, in CD® (SD) rats under the conditions of this study were:

- For parental systemic toxicity: 75 ppm
- For parental reproductive toxicity: 1500 ppm
- For offspring toxicity: 75 ppm

The details of this study will be discussed below in the supporting 'Discussion Section'.

Page: 3 continued on page 4 Paragraph: 5 Lines: 4 -7

EPA comment:

In the developmental neurotoxicity study, maternal toxicity was observed at the same dose as changes in brain morphometric measurements in offspring; however, these brain measurements were not performed at the next lower dose and consequently, there is some uncertainty about the NOAEL for this effect.

Aventis' response:

As stated above, Aventis has submitted to EPA a revised DNT, which demonstrated no alterations in brain morphometric measurements taken in the offspring, thus no increased sensitivity was observed in the pups. The details of this study will be discussed below in the supporting 'Discussion Section'.

Page: 4 Paragraph: 5 - continuation from page 3 Lines: 2 -9

EPA comment:

The 10x Food Quality Protection Act (FQPA) Safety Factor has been retained because: 1) the toxicology data base is incomplete; there is a data gap for the multi-generation reproduction study in rats; 2) an assessment of susceptibility following pre-/post-natal exposure to carbaryl could not be made due to the data gap for the reproduction study; 3) there is concern for the results of the developmental neurotoxicity study (uncertainty about NOAEL). Based on these considerations, the 10x safety factor was applied to all population subgroups in assessing risks from acute and chronic dietary exposures and residential exposures of all durations.

Aventis' response:

As stated above, Aventis has submitted to EPA a revised DNT and a new 2-Generation Reproduction Study that has a direct impact on the FQPA Safety Factor. Aventis firmly believes that with the submission of these two studies, the data gap for the 2-generation reproduction study will be fulfilled and the NOEL question for the DNT will be resolved. Thus, the Agency has the required data to reduce the FQPA Safety Factor from 10X to 1X.

Page: 4 Paragraph: 1 Lines 1-6:

EPA comment:

Carbaryl has been classified as a Group C possible human carcinogen based on an increased incidence of hemangiosarcomas and combined hemangiomas/hemangiosarcomas in CD-1 mice at 1000 ppm (146 mg/kg/day) and above. Mechanistic metabolism studies and a study in heterozygous p53-deficient mice were considered inadequate to demonstrate a mode of action for the vascular tumors. The default linear low dose extrapolation was used for risk assessment; the Q_1* is 1.19×10^{-2} $(mg/kg/day)^{-1}$ based on the mouse vascular tumors.

Aventis' response:

Aventis strongly believes that the use of carbaryl products presents no imminent carcinogenic risk to users based on the following points:

- Current data support a hypothesis that high doses of carbaryl in life-time studies produce tumors via a non-genotoxic mechanism, possibly related to altered metabolism at these high doses.

- At doses less than the MTD, there was an increased incidence of tumors only in 1 site of 1 sex of 1 species.

- The increased incidence of vascular tumors in the male mice after two years of administration is of questionable biological significance.

- In the p53 knockout mouse model, which was demonstrated, to be sensitive to the induction of vascular tumors by a genotoxic reference compounds, carbaryl was found to be negative.

- The weight-of-the evidence indicates that carbaryl shows no potential for genotoxicity

- Epidemiological data on carbaryl production workers show no increase in tumor incidence.

In the two-year bioassay conducted in the CD1 mouse, a statistically significantly higher incidence of vascular tumors was noted in males at 1,000 and 8,000 ppm. In females, no statistically significant change in the incidence of vascular tumors was observed. The overall incidence of vascular tumors was 2, 6, 10 and 10 in males and 3, 3, 4 and 9 in females at 0, 100, 1,000 and 8,000 ppm, respectively.

In order to address the biological significance of the vascular tumors, the p53 knockout mouse model was used as a tool to study chemical carcinogenesis (Donehower, 1996). The p53 mouse is a genetically manipulated mouse in which one allele of the p53 tumor suppresser gene has been inactivated. One of the assumptions with the knockout model is that a mutation at the intact p53 allele is necessary for the development of the carcinogenic process. In principle non-genotoxic compounds, which induce tumors by other mechanisms should not induce tumors in this system. The p53 knockout mouse model was validated by testing two compounds: urethane, a genotoxic compound known to produce vascular tumors in standard carcinogenicity bioassays, and d-limonene, which is neither genotoxic nor carcinogenic in mice but which is known to be carcinogenic in the male rat by a well described non-genotoxic mechanism. In the validation study, the p53 model proved to be very efficient for the induction of vascular tumors by genotoxic compounds (Bigot, 1999; Carmichael et al. 1999). Therefore, this model will produce an unambiguous response to specifically identify genotoxic compounds.

Therefore, carbaryl was tested in the p53 mouse. The objectives of the studies were to evaluate if carbaryl would induce vascular tumors in this model and to set a NOEL in this sensitive and specific model. Additionally, this model provides evidence that the tumors observed in the standard carcinogenicity bioassays resulted from an indirect genotoxic effect.

Carbaryl was administered continuously via the diet to groups of 20 male heterozygous p53 knockout mice at concentrations of 0, 10, 30 100, 300, 1,000 and 4,000 ppm for at least 180 days. At the end of the study, all animals were necropsied, selected organs weighed and a range of tissues were taken, fixed and examined microscopically. Carbaryl did not induce mortalities or clinical signs related to the treatment. Only a slight decrease in food consumption during the first eight weeks was observed at 4,000 ppm. This observation was correlated with a lower body weight evolution in comparison with the control animals.

No tumors were found in the 4,000 ppm group. In the other treated groups, a few sporadic tumors were found, but they were clearly unrelated to treatment and representative of the spontaneous tumor types present in mice of this age and strain. In particular, it should be noted that no tumors were found in the liver, kidney or vascular system, which were seen in the original mouse oncogenicity study with carbaryl. The only treatment-related non-proliferative change observed was the presence of globular deposits in the umbrella cell layer of the urinary bladder at 100 ppm or more.

In conclusion, the data from the p53 studies, the following conclusion can be made:

1). The p53 model was validated with urethane one of the few compound known to induce specifically vascular tumors.
2). Carbaryl was negative, and also did not accelerate the formation of any other tumor types.
3). There is a clear NOEL at 4000 ppm (approximately 716 mg/kg b.w./day) in the p53 mouse study for carcinogenicity.
4). Carbaryl is not a genotoxic carcinogen.

Thus the weight-of-the evidence indicates that carbaryl is not a genotoxic agent in humans. In addition, epidemiological data on carbaryl production workers show no increase in tumor incidence. The two epidemiology studies of Aventis CropScience (formerly Rhône-Poulenc and Union Carbide) factory workers representing a sub-population of the general public with the highest exposure (i.e., exposure on a daily basis over many years). Thus, the data from these studies represent a potential "worst-case" for chronic carbaryl exposure to humans. The results from these studies show that the overall mortality experience of the cohort is significantly less than expected when compared to both United States and West Virginia male death rates. In general, these studies support conclusion that there were no excess cases of cancer in this working population.

A further discussion of this study and the entire carcinogenicity issue will be discussed below in the supporting ‘Discussion Section’.

Page: 4 Paragraph: 2 Lines 5-12:

EPA comment:

The toxicity endpoints selected for risk assessment are based on neurotoxic effects of ChEI. The dose levels used for the acute and chronic dietary risk assessment, i.e. 10 mg/kg and 3.1 mg/kg/day, were both from studies (acute neurotoxicity study in the rat and chronic toxicity study in the dog, respectively) in which a NOAEL was not determined. Therefore, an additional uncertainty factor of 3x was added to the customary 100x uncertainty factor [10x for extrapolation from animal studies to humans and 10x for intraspecies (human) variation]. The acute and chronic reference doses were 0.03 mg/kg and 0.01 mg/kg/day, respectively.

Aventis' response:

Concerning the acute neurotoxicity study in rats, Aventis does not disagree with the Agency's assessment for this endpoint. However, for the chronic study in dogs, Aventis does not agree with the additional 3X for a lack of a NOEL in the study. According to the policy issued in August 2000 concerning the endpoint for selection for cholinesterase inhibiting compound, the Agency stated that the red blood cell (RBC) should be used instead of the plasma. The NOEL for RBC cholinesterase inhibition was 125 ppm (3.1 mg/kg/day). Additionally, Aventis believes that the brain cholinesterase inhibition observed at the 125 ppm level are slightly above background level and were not of toxicological concerns due to the lack of clinical signs observed at this dose level. Furthermore, Aventis performed a five-week study in dogs, which agreed with the results of the chronic study. Therefore, it is our opinion that all calculations based on the chronic dog in the document should be adjusted to reflect the removal of the 3X safety factor.

Page: 4 Paragraph: 2 Lines 1-6:

EPA comment:

No dermal or inhalation studies were available.

Aventis' response:

As part of the 60-day public comment period, Aventis will be submitting three 21-day dermal studies, which cover the technical material and the formulated products SEVIN® XLR, and SEVIN® 80S. The study results will not be available in time to provide the information to the Agency as part of the 30-day comment period. Similarly, Aventis will be submitting comments for the inhalation requirement as part of the 60-day public comment period. However, it should be noted that in the document titled, "Carbaryl: Toxicology Chapter For RED" the inhalation study was not listed as a data gap on page 25 of that document.

Page: 8 Paragraph: 3 Lines 1-10:

EPA comment:

HED calculated the risks of carbaryl exposure in tobacco. Based on a pyrolysis study submitted by the registrant, residues of carbaryl total approximately 44.58 ppm in tobacco smoke (side-stream and main-stream combined). Since this is a composited sample of main-stream and side-stream smoke, it greatly exaggerates the actual exposure to the smoker, whose primary route of exposure is via main-stream smoke. HED further assumed that 100% inhaled is absorbed (i.e., that none of the residue is exhaled along with the smoke). These assumptions result in an extreme overestimate of actual likely exposure. Comparing exposure to the short-term inhalation Lowest-Observable-Adverse-Effects-Level (LOAEL) of 10 mg/kg/day, the short-term MOE for carbaryl exposure from the use of tobacco is estimated to be 1000 for males and 900 for females. The MOEs are less than the residential short-term inhalation target MOE of 3000 and therefore, the risks exceed HED's level of concern for the general population.

Aventis' response:

The relative risk of carbaryl, which is not a genotoxic agent, as compared to the many direct acting genotoxic agents contained in main- and side-stream smoke is insignificant and is not calculable. The calculation presented by the Agency is crude at best and does not have any impact on the relative risk of smoking cigarettes.

Page: 10 Paragraph: 2 Lines 1-18:

EPA comment:

HED evaluated reports of human carbaryl poisonings and adverse reactions associated with its use from the following sources: OPP Incident Data System (IDS); Poison Control Centers' Toxic Exposure Surveillance System; California Department of Pesticide Regulation; the National Pesticide Telecommunications Network (NPTN); open literature; and an unpublished study submitted by the registrant. The data from IDS indicated that a majority of cases from carbaryl exposure involved dermal reactions. A number of other cases involved asthmatics and people who experienced hives and other allergic type reactions. It is noted that the dermal sensitization study in the guinea pig was negative. Reports of allergic-type reactions in humans could be evidence of a difference in species sensitivity or could be attributable to inert ingredients in the marketed formulations. According to California data, about half have the cases involved skin and eye effects in handlers. About a quarter of the skin reactions were due to workers that were exposed to residues on crops. Reports from the literature are very limited but tend to support the finding that carbaryl has irritant properties. The Poison Control Center cases involving non-occupational adults and older children showed an increased risk in five of the six measures used for comparing carbaryl incidents to all other pesticides. The carbaryl cases were almost twice as likely to require serious health care (hospitalization or treatment in a critical care unit) and were two and a half times more likely to experience major medical

outcome (life-threatening effects or significant residual disability) than other pesticides. This pattern of increased risk was not seen among occupational reports or in young children. This may mean that careless handling by non-professionals is a particular hazard.

Aventis' response:

As stated by the Agency, reports from the literature are very limited. To draw such conclusions that carbaryl cases were almost twice as likely to require serious health care (hospitalization or treatment in a critical care unit) and were two and a half times more likely to experience major medical outcome (life-threatening effects or significant residual disability) than other pesticides is speculative and goes too far in assigning increased frequency values based on limited and often unconfirmed information. The reports cited by the Agency from poison control centers are difficult to interpret because the relative causative agent is frequently not identified. If the agent is identified by officials, the majority of the time it is stated by the officials that the causative agent is merely speculation on their part and that the real agent is not readily known with great certainty.

According to test conducted by Aventis on both technical grade and formulation products, carbaryl is not a skin sensitizer. Furthermore, epidemiological data on carbaryl production workers showed no pattern of skin reaction. This would indicate that if the product is used according to the label, the relative risks of skin reactions to carbaryl are very low.

Page: 10 Paragraph: 3 Lines 1-5:

EPA comment:

Five case report studies suggested that carbaryl might be a cause of chronic neurological or psychological problems. Some of these effects appear to be consistent with those reported from organophosphate poisoning. However, unlike organophosphates, no controlled studies have been undertaken. If such effects occur as a result of over-exposure to carbaryl, they appear to be relatively rare. The effects reported among the five case reports are too inconsistent to draw any conclusions, but do suggest the need for further study.

Aventis' response:

Aventis agrees with the Agency that the five case studies cited are weak at best and that the Agency should not be drawing any conclusions based on such inconsistent data. The discussion of such data will lead the reader to draw inappropriate conclusions. Furthermore, epidemiological data on carbaryl production workers showed no such pattern and would indicate that if the product is used according to the label, the relative risks of carbaryl are very low.

Page: 11 Paragraph: 1 Lines 1-3:

EPA comment:

The epidemiologic study submitted by the registrant compared mortality rates in plant workers exposed to carbaryl to the general population. HED concluded that

the sample of workers was too small and the period of follow-up too short to permit definitive conclusions.

Aventis' response:

Aventis disagrees with the Agency that the mortality rates in plant workers exposed to carbaryl cannot be translated to the general population. The study was statistically designed to specifically address this concern and to examine other non-mortality endpoints. The two epidemiology studies of Aventis CropScience (formerly Rhône-Poulenc) factory workers representing a sub-population of the general public with the highest exposure (i.e., exposure on a daily basis over many years). Thus, the data from these studies represent a potential "worst-case" for chronic carbaryl exposure to humans. The results from these studies show that the overall mortality experience of the cohort is significantly less than expected when compared to both United States and West Virginia male death rates. In general, these studies support conclusion that there were no excess cases of cancer in this working population.

Page: 11 Paragraph: 4 Lines 2-4:

EPA comment:

However, certain key information, which would help refine the risk assessment, is missing. Toxicology data gaps include a reproduction study, a 21-day dermal study in the rat, a 90-day inhalation study in the rat and a micronucleus study.

Aventis' response:

The Agency has previously granted a wavier for the in vivo cytogenicity/micronucleus. Furthermore, Aventis has fulfilled the data requirement for the in vivo mouse micronucleus study. Aventis believes that repeating the in vivo mouse micronucleus study is not appropriate based on the fact that the top dose in the currently submitted mouse micronucleus was 200 mg/kg/day and was similar to the mid-dose of 250 mg/kg/day tested in an acute gavage study in mice. At the 250 mg/kg dose level tested in the acute study plasma, RBC, and brain cholinesterase inhibition was seen. The percent cholinesterase inhibition observed was 45.7, 45.7, and 57.8, respectively. At the highest dose tested (500 mg/kg) in the acute study, percent cholinesterase inhibition for plasma, RBC, and brain was 59.8, 57.1, and 66.6, respectively. Additionally, the clinical signs observed at both the 250 and 500 mg/kg dose levels were very similar in both findings and incidences. Repeating the mouse micronucleus study at a slightly higher dose level would not result in an increase in significant clinical signs. Therefore, the base results of the study concerning clastogenic or aneugenic effects would not change. Carbaryl is not mutagenic for these endpoints.

As previously indicated in this document, Aventis will be submitting three 21-day dermal studies which cover the technical material and for the formulated products SEVIN XLR and SEVIN 80S. Similarly, Aventis will be submitting comments for the inhalation requirement as part of the 60-day public comment period.

However, it should be noted that in the document titled, "Carbaryl: Toxiccology Chapter For RED" the inhalation study was not listed as a data gap on page 25 of that document.

Section Number 3.0
Hazard Profile

Page: 14-15 Paragraph: 1 Lines: 1-10

EPA comment:

The Toxicology Chapter of the RED was prepared by Dr. Virginia Dobozy (D240992 dated December 13, 1999). The toxicology database is of good quality; however, it is incomplete. The following studies are required: two-generation reproduction study, 21-day dermal toxicity study with cholinesterase measurements, 90-day inhalation study with cholinesterase measurements and micronucleus study. The lack of a reproduction study and some uncertainty about the findings in offspring in the developmental neurotoxicity study are obstacles to assessing special sensitivity of infants and children and as such, the 10x FQPA Safety Factor was retained. However, the database provides sufficient information for selecting toxicity endpoints for risk assessment and therefore, supports a reregistration eligibility decision for the currently registered uses.

Aventis' response:

As stated previously, Aventis has submitted to EPA a revised DNT and a new 2-Generation Reproduction Study, which have a direct impact on the FQPA Safety Factor. Aventis firmly believes that with the submission of these two studies, the data gap for the 2-generation reproduction study is fulfilled and the DNT NOEL question will be resolved. Thus, the Agency has the required data to reduce the FQPA Safety Factor from 10X to 1X. As for the 21-day dermal, 90-day inhalation and mouse micronucleus studies, the need for these studies is addressed in the previous comments made by Aventis.

Page: 17 Paragraph: 1 Lines: 1-6

EPA comment:

In the developmental neurotoxicity study, clinical signs of toxicity and plasma and brain ChEI were seen in maternal animals at the same dose (10 mg/kg/day) as changes in brain morphometric measurements (decreases in cerebellar measurements in females on Day 11 post-partum) were observed in offspring; however, brain measurements were not conducted at the next lower dose. The lowest NOAEL after a single dose administration in adult animals was for maternal animals in the developmental neurotoxicity study, i.e., 1 mg/kg/day.

Aventis' response:

Aventis has submitted to EPA a revised DNT Study, which demonstrated that no alterations in brain morphometric measurements were observed in the offspring, thus no increased sensitivity was observed in the pups. The details of this study

will be discussed below in the supporting 'Discussion Section'.

Page: 17 Paragraph: 2 Lines: 1-3

EPA comment:

No subchronic studies in the rat or dog are available, except for the subchronic neurotoxicity study in rats. The chronic toxicity data showed that, in dogs, decreases in plasma, RBC and brain ChE were observed at 10 mg/kg/day; clinical signs of toxicity were also observed in both sexes.

Aventis' response:

For the chronic study in dogs, Aventis does not agree with the additional 3X for a lack of a NOEL in the study. According to the policy issued in August 2000 concerning the endpoint for selection for cholinesterase inhibiting compound, the Agency stated that the RBC should be used instead of the plasma. The NOEL for RBC cholinesterase inhibition was 125 ppm (3.1 mg/kg/day). Additionally, Aventis believes that the brain cholinesterase inhibition observed at the 125 ppm level is slightly above background level and was not of toxicological concerns due to the lack of clinical signs observed at this dose level. Furthermore, Aventis performed a five-week study in dogs, which agreed with the results of the chronic study. Therefore, it is our opinion that all calculations based on the chronic dog in the document should be adjusted to reflect the removal of the 3X safety factor.

Page: 17 Paragraph: 3 Lines: 1-21

EPA comment:

The Health Effects Division's (HED) Cancer Peer Review Committee (CPRC)(12/8/93) classified carbaryl as a Group C - possible human carcinogen based on an increased incidence of hemangiosarcomas and combined hemangiomas/ hemangiosarcomas in male mice. Both the low dose extrapolation (Q_1*) and margin of exposure (MOE) approaches were proposed for risk assessment. In addition, an RfD approach would be provided to assess the most sensitive non-cancer health endpoint for comparison to the linear and MOE approaches. The CPRC requested additional metabolism studies, which could 1) direct the selection of the more appropriate quantitative approach; and 2) provide insight into the significance of the tumors seen only at excessively toxic doses. Additional metabolism studies, including mechanistic studies, were submitted subsequent to the 1993 meeting. A subgroup of the Cancer Assessment Review Committee (CARC) met on September 3, 1998, to review the metabolism studies and concluded that the data from all available metabolism studies were not adequate to support a nonlinear mode of action, as described in the 1996 *EPA Proposed Guidelines for Carcinogen Risk Assessment*, and therefore recommended that the default linear approach should be used for the cancer risk assessment. The revised Q_1*, based on the CD-1 mouse dietary study with ¾ Interspecies Scaling Factor, is 1.19×10^{-2} $(mg/kg/day)^{-1}$ in human equivalents. Subsequently, the registrant submitted a special study in genetically modified mice. Carbaryl was administered to heterozygous p53-deficient (knockout) male mice in the diet at concentrations of up to 4000 ppm (716.6 mg/kg/day) for six

months. There was no evidence of neoplastic or preneoplastic changes in the vascular tissues of any organ. A model validation study demonstrated that vascular tumors occur in heterozygous p53 deficient mice within six months of administration of a known genotoxic carcinogen (urethane).

Aventis' response:

Aventis strongly believes that the use of carbaryl products presents no imminent carcinogenic risk to users based on the following points:

- Current data support a hypothesis that high doses of carbaryl in life-time studies produce tumors via a non-genotoxic mechanism, possibly related to altered metabolism at these high doses.

- At doses less than the MTD, there was an increased incidence of tumors only in 1 site of 1 sex of 1 species.

- The increased incidence of vascular tumors in the male mice after two years of administration is of questionable biological significance.

- In the p53 knockout mouse model, which was demonstrated, to be sensitive to the induction of vascular tumors by a genotoxic reference compounds, carbaryl was found to be negative.

- The weight-of-the evidence indicates that carbaryl shows no potential for genotoxicity

- Epidemiological data on carbaryl production workers show no increase in tumor incidence.

As background, in the two-year bioassay conducted in the CD1 mouse, a statistically significantly higher incidence of vascular tumors was noted in males at 1,000 and 8,000 ppm. In females, no statistically significant change in the incidence of vascular tumors was observed. The overall incidence of vascular tumors was 2, 6, 10 and 10 in males and 3, 3, 4 and 9 in females at 0, 100, 1,000 and 8,000 ppm respectively.

In order to address the biological significance of the vascular tumors, the p53 knockout mouse model was used as potential tool to study chemical carcinogenesis (Donehower, 1996). The p53 mouse is a genetically manipulated mouse in which one allele of the p53 tumor suppresser gene has been inactivated. One of the assumptions with the knockout model is that a mutation at the intact p53 allele is necessary for the development of the carcinogenic process. In principle non-genotoxic compounds, which induce tumors by other mechanisms should not induce tumors in this system. The p53 knockout mouse model was validated by testing two compounds: urethane, a genotoxic compound known to produce vascular tumors in standard carcinogenicity bioassays, and d-limonene,

which is neither genotoxic nor carcinogenic in mice but which is known to be carcinogenic in the male rat by a well described non-genotoxic mechanism. In the validation study, the p53 model proved to be very efficient for the induction of vascular tumors by genotoxic compounds (Bigot, 1999; Carmichael et al. 1999). Therefore, this model will produce an unambiguous response to specifically identify genotoxic compounds.

Therefore, carbaryl was tested in the p53 mouse. The objectives of the studies were to evaluate if carbaryl would induce vascular tumors in this model and to set a NOEL in this sensitive and specific model. Additionally, this model provides evidence that the tumors observed in the standard carcinogenicity bioassays resulted from an indirect geneotoxic effect

Carbaryl was administered continuously via the diet to groups of 20 male heterozygous p53 knockout mice at concentrations of 0, 10, 30 100, 300, 1,000 and 4,000 ppm for at least 180 days. At the end of the study, all animals were necropsied, selected organs weighed and a range of tissues were taken, fixed and examined microscopically. Carbaryl did not induce mortalities or clinical signs related to the treatment. Only a slight decrease in food consumption during the first eight weeks was observed at 4,000 ppm. This observation was correlated with a lower body weight evolution in comparison with the control animals.

No tumors were found in the 4,000 ppm group. In the other treated groups, a few sporadic tumors were found, but they were clearly unrelated to treatment and representative of the spontaneous tumor types present in mice of this age and strain. In particular, it should be noted that no tumors were found in the liver, kidney or vascular system, which were seen in the original mouse oncogenicity study with carbaryl. The only treatment-related non-proliferative change observed was the presence of globular deposits in the umbrella cell layer of the urinary bladder at 100 ppm or more.

In conclusion, the data from the p53 studies, the following conclusion can be made:

1). The p53 model was validated with urethane one of the few compound known to induce specifically vascular tumors.
2). Carbaryl was negative, and also did not accelerate the formation of any other tumor types.
3). There is a clear NOEL at 4000 ppm in the p53 mouse study for carcinogenicity.
4). Carbaryl is not a genotoxic carcinogen.

Thus the weight-of-the evidence indicates that carbaryl is not a genotoxic agent in humans. In addition, epidemiological data on carbaryl production workers show no increase in tumor incidence. The two epidemiology studies of Aventis CropScience (formerly Rhône-Poulenc) factory workers representing a sub-

population of the general public with the highest exposure (i.e., exposure on a daily basis over many years). Thus, the data from these studies represent a potential "worst-case" for chronic carbaryl exposure to humans. The results from these studies show that the overall mortality experience of the cohort is significantly less than expected when compared to both United States and West Virginia male death rates. In general, these studies support conclusion that there were no excess cases of cancer in this working population.

Page: 18 Paragraph: 1 Lines: 1-8

EPA comment:

Carbaryl was not mutagenic in the *Salmonella typhimurium* assay or genotoxic in the Unscheduled DNA Synthesis assay. In a chromosomal aberration test using Chinese Hamster Ovary (CHO) cells, carbaryl was clastogenic in the presence of S9 activation. The CPRC (1993 meeting) required an *in vivo* cytogenetics study in rodents to provide insight into the structural and/or numerical aberrations in the study. The mouse micronucleus study submitted to satisfy this requirement was deemed unacceptable. HED concluded that, based on a Weight of the Evidence assessment, the database does not support that carbaryl acts as a DNA-reactive mutagen. However, this alone is not sufficient to demonstrate a mode of action for establishing a threshold cancer risk assessment.

Aventis' response:

The Agency has previously granted a wavier for the in vivo cytogenicity/micronucleus. Furthermore, Aventis has fulfilled the data requirement for the in vivo mouse micronucleus study. Aventis believes that repeating the in vivo mouse micronucleus study is not appropriate based the fact that the top dose in the currently submitted mouse micronucleus was 200 mg/kg/day and was similar to the mid-dose of 250 mg/kg/day tested in an acute gavage study in mice. At the 250 mg/kg/day dose level tested in the acute study plasma, RBC, and brain cholinesterase inhibition was seen. The percent cholinesterase inhibition observed was 45.7, 45.7, and 57.8, respectively. At the highest dose tested (500 mg/kg) in the acute study, percent cholinesterase inhibition for plasma, RBC, and brain were 59.8, 57.1, and 66.6, respectively. Additionally, the clinical signs observed at both the 250 and 500 mg/kg were very similar in both findings and incidences. Repeating the mouse micronucleus study at a slightly higher dose level would not result in an increase in significant clinical signs. Therefore, the base results of the study concerning clastogenic or aneugenic effects would not change. Carbaryl is not mutagenic for these endpoints.

Page: 18 Paragraph: 6 Lines: 1-8

EPA comment:

The FQPA Safety Committee concluded at meetings on November 29, 1999 and April 16, 2001, that the 10x safety factor should be retained because: 1) the toxicology data base is incomplete; there is a data gap for the multi-generation reproduction study in rats; 2) an assessment of susceptibility following pre-/post-

natal exposure to carbaryl could not be made due to the data gap for the reproduction study; 3) there is concern for the results of the developmental neurotoxicity study (uncertainty about NOAEL/LOAEL for brain morphometric alterations). The Committee concluded the 10x safety factor should be applied to all population subgroups when assessing acute and chronic dietary exposures and residential exposures of all durations.

Aventis' response:

As stated above, Aventis has submitted to EPA a revised DNT Study and a new 2-Generation Reproduction Study which will have a direct impact on the FQPA Safety Factor. Aventis firmly believes that with the submission of these two studies, the data gap for the 2-generation reproduction study will be fulfilled and clarification of the DNT NOEL issue will be provided. Thus the Agency has the required data to reduce the FQPA Safety Factor from 10X to 1X.

SUPPORTING DISCUSSIONS

Supplemental Developmental Neurotoxicity Study Findings

The document submitted to EPA describes the supplemental histomorphometric evaluation performed on the cerebellum of rat pups and adults from the carbaryl developmental neurotoxicity study (Robinson and Broxup 2001). This additional work was conducted in response to the EPA review of the study final report. In that review, EPA indicated that the bilateral decrease in the length of the cerebellum accompanied by a non-statistically significant 5% decrease in cerebellar weights in the day 11 females and the bilateral increase in the width of the cerebellum in the day 70 female animals at the highest tested dose (10 mg/kg/day) may possibly be treatment related. Further, some forebrain measurements may have also been affected. In order to clarify the treatment relationship of these findings, the Agency recommended that additional morphometric measurements be performed to support the NOEL and that the thickness of the cellular layers in the cerebellum be more fully described.

The submitted report addresses the EPA comments by presenting additional evaluations of the high dose animals, only. The evaluations clearly demonstrate that there are no treatment-related morphometric findings in the cerebellum of male and female pups and adults. These findings are in agreement with the results from the high dose group animals in the study final report that found no treatment-related changes in: **1)** Brain weights in male and female pups; **2)** Cerebellar weights in male and female pups; **3)** Terminal body weights in male and female pups; **4)** Brain weights in male and female adults; **5)** Terminal body weights in male and female adults; **6)** FOB measurements and motor activity in male and female pups; **7)** Motor activity, auditory startle response, passive avoidance, and water maze measurements in male and female adults.

The evaluations clearly demonstrate there are no treatment related morphometric alterations of the cerebellum in male and female pups or adults treated with carbaryl at a dose of 10 mg/kg/day, from Day 6 of gestation to Day 10 *post-partum*, inclusively. In addition, in the forebrain no measurable bilateral differences are detected between control and carbaryl exposed pups and adults.

In conclusion, carbaryl did not induce any morphologic or morphometric changes in either the cerebellum or the forebrain in animals receiving a high dose of 10 mg/kg/day. As described, the new morphometric results revealed no changes at the high dose, are in agreement with the lack of treatment-related effects on terminal body, brain, and cerebellar weights, as well as behavioral and motor activity tests in male and female pups and adults.

2-Generation Reproduction Study Findings

A 2-Generation reproduction study with carbaryl technical was completed at Research Triangle Institute located in North Carolina, USA, in order to provide information on the influence of carbaryl technical on the reproductive performance in rats (Tyl et al. 2001). The purpose of this study was to evaluate the potential of carbaryl, administered in the feed to CD rats, to produce alterations in parental fertility, maternal pregnancy and lactation, and growth and development of the offspring for two generations, one litter per generation. This study was performed in compliance with U.S. EPA FIFRA GLP Standards (U.S. EPA, 1989), the U.S. EPA OPPTS Testing Guidelines (U.S. EPA, 1998), and the OECD testing guidelines for a two-generation reproductive toxicity study (OECD, 1983).

Male and female CD® (Sprague-Dawley) rats (the FO generation) were administered carbaryl (1-naphthyl methylcarbamate; CAS No. 63-25-2) in the feed at 0, *75,* 300, and 1500 ppm, available *ad libitum,* 30 animals/sex/dose, for ten weeks. Body weights and feed consumption were recorded weekly, and clinical signs were recorded at least once daily. Vaginal cytology was evaluated for the last three weeks of the prebreed period. Animals were then randomly mated within treatment groups for a two-week mating period to produce the Fl generation, with exposure continuing. FO males were necropsied after the delivery period, with histological evaluation of reproductive and other organs and andrological assessments (reproductive organ weights, epididymal sperm number, motility and morphology, testicular homogenization-resistant spermatid head counts, daily sperm production, and efficiency of daily sperm production). Fl litters were culled to ten pups on postnatal day (pnd) 4 and weaned on pnd 21. At weaning, up to three weanlings/sex/litter were necropsied, and 30/sex/dose were selected as Fl parents of the F2 generation. FO females were then necropsied with organ weights, stage of estrus at necropsy, enumeration of ovarian primordial follicles, and histopathology of reproductive and other selected organs. Selected Fl weanlings, 30/sex/dose, were administered carbaryl in the diet for a ten-week prebreed exposure period, with acquisition of vaginal patency in females and preputial separation in males assessed, and vaginal cytology for estrous cyclicity in Fl selected females evaluated during the last three weeks of the prebreed exposure period. They were mated for a two-week period, as described above. At weaning of F2 litters, up to three weanlings/sex/litter were necropsied. Fl males were necropsied after the delivery period, with histopathology and andrological assessments (as described above). At weaning of the F2 litters, parental Fl females were then necropsied with histopathology, as described above, and F2 weanlings, up to three/sex/litter, were necropsied.

Dietary exposure to carbaryl for two generations, one litter per generation, at 0, *75,* 300, and 1500 ppm, resulted in: decreased body weights and decreased weight gains in P0 and P1 parental males and females, accompanied by decreased feed consumption at 1500 ppm, and slightly reduced body weights and feed consumption at 300 ppm; Fl and P2 offspring toxicity (reduced body weights during lactation beginning on post-natal day (pnd) 4 through lactation and continuing in selected P1 offspring through acquisition of puberty) at 1500 ppm; increases in P1 pup mortality at 1500 ppm and in P2 pup mortality

at 300 ppm and 1500 ppm during lactation, especially early (pnd 0-4), accompanied by reduced maternal body weights in FO and P1 dams at 1500 ppm and 300 ppm, and delayed vaginal opening and preputial separation in selected Fl offspring at 1500 ppm considered an indirect effect related to body weight decreases.

In conclusion, the NOELs for carbaryl administered in the diet, in CD® (SD) rats under the conditions of this study, were:

- parental systemic toxicity: 75 ppm
- parental reproductive toxicity: 1500 ppm
- offspring toxicity: 75 ppm

EPIDEMIOLOGIC DATA - Epidemiological data on carbaryl: standardized mortality ratio analysis of employees exposed to carbaryl at the Rhône-Poulenc Institute, West Virginia plant.

The National Institute of Occupational Safety and Health (NIOSH) and the Union Carbide Corporation (UCC) on chemical production plants in the Kanawha Valley (KV) of West Virginia originally initiated an epidemiological study. One of the plants included in this extensive epidemiology study was the facility at which carbaryl is produced in Institute, West Virginia. The plant was acquired by Rhône-Poulenc (now Aventis CropScience) from UCC in December 1986.

The study (Pastides 1993) reported here investigated the total and cause-specific mortality experience of employees exposed to carbaryl at the production plant. No additional information other than what was available in the original database was collected about the health or mortality experience of individuals employed at this plant for this study. The central results of this report were presented in terms of Standardized Mortality Ratios (SMR's) and 95% confidence intervals (95% CI's).

Carbaryl technical is manufactured, packaged, and shipped from the Aventis CropScience plant in Institute, West Virginia. Besides carbaryl, the plant also produces other agricultural products. In the past, numerous other chemical compounds were produced there, including butanol, styrene, acetaldehyde, toluene, fluorocarbons and others.

Carbaryl is produced in crystalline form, as well as in an oil-based solution (41% carbaryl). Final processing includes crystallizing, drying, bin storage, and packing. Exposure to carbaryl would occur among three basic categories of employees: those in the manufacturing unit, those in maintenance, and those in packaging and distribution.

For employees of the carbaryl unit, UCC tracked through 1988 the vital status, and cause of death information, of all individuals who were <u>first</u> <u>hired</u> between the start-up of the carbaryl unit in 1960 through 1978. Employees hired after 1978 were not part of the NIOSH/UCC KV study.

Using the KV database, UCC conducted SMR analyses of the employees from the entire Institute plant in the past. However, no separate examination of data from employees specifically exposed to carbaryl was made. In the overall Institute study, no excess risk in total mortality, total cancer mortality, or site-specific cancer mortality, was observed.

In the carbaryl specific study, a total of 522 employees were identified within the UCC database as belonging to one of the three-carbaryl exposure groups; (158-Carbaryl Production, 229-Packing and Distribution, 327-Maintenance)

Because of some overlap between the groups and because some individuals did not meet the NIOSH/UCC cohort entry criteria, the final number of employees available for the SMR analysis was 488. These 488 employees contributed 7,531.5 person-years to the mortality analysis. This number represents the combined number of years in which these employees were followed through 1988.

As of the end of 1988, twenty-five deaths were identified from this cohort of employees. Elevated SMR's, reflecting an observed number of deaths greater than the number expected were seen for cancer of the pancreas, cancer unspecified, and cancer of the brain and other parts of the nervous system. In the former two categories, the excess was slight and based on only a single death; furthermore the wide confidence intervals suggest a relatively imprecise SMR estimate and one that is well within the range of chance variation. In the case of brain and nervous system cancer, the higher SMR suggested a possibility of some association with work in the carbaryl unit, yet the very wide confidence interval indicates that the SMR estimate has low precision. In other words, the estimate is unstable, is within the range of chance variation, and reflects the small sample size on which it is based. Furthermore, review of the death certificates of these two individuals revealed that these tumors were of different histologic origin; one was reported as an astrocytoma, the other as a glioblastoma multiforme. This information reduces the plausibility that both malignancies were caused by the same exposure.

The next phase of the carbaryl plant worker epidemiology study has been completed (Pastides and Zorn, 1997), and the results are based on vital status of employees through 1994. The new cohort consisted of 817 employees (488 from the previous analysis and 329 who were hired after 1978). Taking into account restriction criteria, as described in the report, the restricted cohort that reflects the number of employees who worked across departments is 599. As previously shown, the overall mortality experience of the cohort is significantly less than expected when compared to both United States and West Virginia male death rates. In general, the follow-up study supported the results from the initial study that there were no excess cases of cancer in this working population.

Carcinogenicity Issue – Historical Perspective and as presented to JMPR and submitted to EPA in 2000

A. Combined Oncogenicity/Chronic Toxicity Studies

1) Carbaryl produced tumors primarily at the highest dose tested.

The dietary concentrations in the rat study were 0, 250, 1500, and 7500 ppm (approximately 13, 75, and 375 mg/kg b.w.); for the mouse study the concentrations of technical carbaryl were 0, 100, 1000, and 8000 ppm (approximately 12, 143, and 1143 mg/kg). The highest doses were chosen to satisfy the U.S. EPA requirement for an MTD, while the lower doses were selected for determining the NOEL and to produce moderate toxicity in tissues and on cholinesterase. Considering an approximate acute oral LD_{50} in rats and mice of 250 mg/kg, these doses would therefore be equivalent to 0.06, 0.6 and 4.6 times the acute oral LD_{50} for mice and 0.05, 0.3 and 1.5 times the acute oral LD_{50} for rats. (The high doses for the mouse and rat, respectively, also would be equivalent on a body weight basis to a 70-kg person consuming approximately 80 grams and 26 grams of technical carbaryl per day for a lifetime.)

These MTD levels caused a significant reduction in body weight and body weight gain in both species, especially early in the study. Several other parameters, such as cholinesterase, were also significantly affected throughout the studies at the top doses. The U.S. EPA in their review of the studies agreed that the highest doses in the mouse and rat study exceeded the MTD. As a result, these MTD levels were deemed inappropriate for chronic testing.

Therefore, the only relevant findings for establishing a carcinogenic classification are the vascular system tumors in male mice.

2) The data supporting the oncogenic potential of carbaryl is equivocal since tumors occurred only at one site of one sex of one species when irrelevant data at doses exceeding the MTD are excluded from consideration.

Rat Study

In the rat carcinogenicity study, carbaryl produced tumors in both sexes (thyroid and bladder in males; liver and bladder in females) but only at the MTD (375 mg/kg). At the low and intermediate doses (13 and 75 mg/kg, respectively) there was no indication of an increased incidence of tumors at any of the sites for which increases occurred at the top dose. Thus, at levels less than the MTD, carbaryl has not produced tumors in rats, whether considering the current study or a previous study in which another rat strain was tested.

Mouse Study

In the mouse carcinogenicity study, carbaryl produced tumors (liver and vascular) in females only at the highest dose tested (1143 mg/kg). At the low and intermediate doses (12 and 143 mg/kg, respectively) there was no indication of an increased incidence of tumors at any of the sites for which increases occurred at the top dose. Thus, at doses less than the MTD, carbaryl did not produce tumors in female mice in the current study or in an older study.

In male mice, carbaryl produced tumors in the vascular system and kidney at the highest dose tested (1143 mg/kg b.w.). At the low and intermediate doses (12 and 143 mg/kg) there was no indication of an increased incidence in kidney tumors. At the low and intermediate doses there was an apparent increase in the incidence of vascular tumors as follows:

Dose (mg/kg)	Male Mouse Vascular Tumors		
	Benign	Malignant	Total
0	1	2	2
12	1	6	7
143	1	9	10
1143	3	7	10

However, despite a nearly 10-fold increase in dose increments, the total tumors observed at the intermediate and high doses were the same. The number of malignant tumors actually was slightly lower at the high dose than at the intermediate dose. Thus, these results show there is no clear linear dose-response relationship from the intermediate dose to the high dose, despite a nearly 10-fold difference in dose increment.

With regard to statistical significance, the performing laboratory indicated that statistical significance was just achieved at the $p<0.05$ levels for the top dose, while the intermediate dose results were just above this level of statistical significance (this result was due to the actuarial-type statistical analysis used for tumor incidence and onset). However, the U.S. EPA and U.K. authorities have performed separate statistical analyses and the tumor incidence at the intermediate dose also was found to fall within statistical significance. Based on the results from the original study report, a NOEL could be established based on the lowest dose tested at approximately 12 mg/kg b.w. However, arguments are made in succeeding sections that 18-month historical control data from the performing laboratory are inadequate to determine if the incidence of tumors at any of these doses is biologically significant.

As previously stated, vascular tumors were produced in the female mice but only at the top dose and with a very similar incidence (N = 9) as observed in the males at the top dose. In most other aspects of the study, e.g., body weight effects, clinical signs, clinical

pathology, etc., the females reacted very similar to males. However, there was no indication of an increased incidence of vascular tumors in females at the low or intermediate doses as was observed in the male mice. Thus, these facts raise questions regarding the biological significance of the vascular tumors, which occurred in the male mice.

3) Adequate historical control data were not available from the laboratory conducting the chronic toxicity and oncogenicity studies.

Historical data from the laboratory at which the mouse oncogenicity study was conducted was only available for studies conducted up to 18 months. Aventis CropScience was not certain if these data accurately reflected the incidence of vascular tumors in 24-month CD-1 mice. Additional information was obtained from other sources and summarized (Klonne, 1995) to compare historical control data from several sources and at several study intervals to that of the data for the carbaryl study. The following key observations were made:

- An increase in the spontaneous vascular tumor incidence appears to occur from 18 to 24 months of age in mice.

- An increase in the spontaneous vascular tumor incidence over the last 10 years may be occurring in CD-1 mice.

- The carbaryl study (a 2-year study) should be compared to historical control data from 2-year old mice generated during the last 10 years.

In general, considering the most relevant historical control data outside of the performing laboratory, the incidences of vascular tumors in major organs (spleen/liver) in male mice at the low and middle doses fall within the historical control ranges.

4) The lack of significant histopathological findings at the one-year interim sacrifice of both the mouse and rat studies did not correlate with the detection of tumors in certain tissues at the end of the study.

To further investigate the mechanism by which carbaryl induced multiple tumors in the rat and the mouse after two years of exposure, a decision was made to re-evaluate the histological slides of target organs from the interim sacrifice after one year of treatment. The purpose of this work was to identify if subtle changes present at one year could explain the appearance of tumors seen at two years.

Histopathological examinations were conducted on the target organs (liver, kidney, thyroid gland, urinary bladder) from the control and high dose groups in rats and/or mice. The review was conducted independently by two of Aventis CropScience's pathologists (Debruyne and Irisarri, 1996).

In the rat, at the end of a 52-week exposure period to carbaryl technical by the dietary

route, the re-evaluation of the histological slides revealed the presence of microscopic changes not previously reported in the bladder (transitional epithelial hyperplasia in both male and females), kidney (pelvic urothelial hyperplasia in males), and thyroid (thyroid follicular hypertrophy in males) and liver (hepatocellular hypertrophy in males and females).

In the mouse, no microscopic changes were detected at the end of the 52-week exposure period.

These new findings prompted the Aventis CropScience to conduct further studies to confirm cell proliferation in the various tissues (associated with positive tumor formation) and to re-examine the histological slides from the chronic toxicity and oncogenicity studies.

5) Oncogenicity and chronic toxicity slide review

Aventis CropScience then commissioned independent pathologists to re-examine the histological slides at the 1-year and 2-year sacrifices from the chronic toxicity and oncogenicity studies to determine what other (if any) discrepancies exist outside of those determined by the Aventis CropScience's internal review. This peer review study was conducted according to US. EPA Peer Review policy guidelines. The results of this review showed no differences from the original study pathologists review.

B. Carcinogenic Mechanism

1) Subsequent to the two-year studies, Aventis CropScience proactively performed in vivo genotoxicity studies.

In response to the results of the mouse oncogenicity study, Aventis CropScience proactively conducted an *in vivo* DNA adduct study in mice at a concentration similar to the top dose used in the two-year carcinogenicity study (i.e., 8000 ppm) to determine if carbaryl caused any genotoxic effects (Sagelsdorff, P. 1994). Results indicated that carbaryl did not interact with the DNA in mice, even at the excessive dose used in the study. Additionally, an *in vivo* rat bone marrow chromosomal aberration study was conducted and showed that carbaryl did not produce chromosomal aberrations at doses up to approximately 50% of the acute oral LD_{50} (McEnaney, 1993). Although there was no indication of genotoxic effects in the rat chromosomal aberration and mouse DNA adduct studies, Aventis CropScience recently conducted an *in vivo* micronucleus study in mice to determine if carbaryl produced aneuploidy in this species. Results from the mouse micronucleus assay again showed no genotoxic effects (Marshall, 1996).

Thus, results from these *in vivo* studies indicate that the mechanism of action of carbaryl in the production of tumors in the two-year oncogenicity studies does not occur via a direct genotoxic effect.

2) The weight-of-the-evidence approach indicates that carbaryl shows little potential as a genotoxin.

There have been nearly 50 literature and Aventis CropScience reports on the genotoxicity of carbaryl. The number of test systems and endpoints is extensive. In neither bacterial nor mammalian cell cultures has carbaryl demonstrated any significant mutagenic potential. In various *in vitro* DNA damage and repair assays there is no convincing evidence to suggest that carbaryl produces DNA damage. While carbaryl has shown some clastogenic potential *in vitro*, these changes occur at or near cytotoxic levels. In addition, studies performed *in vivo,* the mouse DNA adduct and rat chromosomal aberration (previously discussed), a mouse dominant lethal study, and an evaluation for mouse micronucleated polychromatic erythrocytes all have been negative.

The absence of tumor induction in a 6-month carcinogenicity study conducted in the p53 knockout mouse demonstrated that the tumors observed in the standard two-year bioassays in rats and mice are not linked to an indirect genotoxic mechanism.

3) It is possible that altered metabolism from unrealistically high doses of carbaryl plays a significant role in the formation of these tumors.

The results from the metabolism study indicated that the carbaryl was almost completely absorbed and metabolized (approximately 90%) and that there was essentially no difference in the metabolism between the sexes or in the low versus the high dose. Likewise, there was no difference in the metabolism between the single versus multiple doses.

The data also indicated that the low dose was almost completely eliminated in 12 hours and the high dose was almost completely eliminated in 24 hours. Two metabolites, 5,6-dihydro-5, 6-dihydroxy carbaryl and 3,4-dihydro-3, 4-dihydroxy carbaryl were identified to be approximately 8% and 1%, respectively, of the total dose and were found to be primarily conjugated to glucuronide. These metabolites are very likely result from the metabolism of epoxide intermediates. Other metabolites, which were likely formed from the epoxide intermediates, were identified as 5-hydroxycarbaryl (13%) and 4-hydroxycarbaryl (6%) and conjugated carbaryl (3%).

Epoxide intermediates have been proposed to be the proximate carcinogen for several classes of carcinogens. Depending on such factors as the stability of the epoxide intermediate, the ability of the cell to detoxify the epoxide (related to such factors as the available glutathione stores, epoxide hydrase activity, etc.), the excretion pattern of the compound, etc., these reactive intermediates may be routinely handled by the body just like other endogenous epoxides or could be available to react with cellular components. Thus, it is possible that excessively high doses of carbaryl could alter the normal metabolism, distribution, and/or excretion pattern in many different ways, e.g., saturate the normal metabolic pathways with a shift of carbaryl metabolism through the epoxide

intermediates, deplete the available glutathione stores available for conjugation, increase the half-life of the epoxide intermediates, increase tissue concentrations of carbaryl and its metabolites due to diminished ability for excretion, etc. Additionally, saturation of many enzyme systems with large carbaryl substrate concentrations could allow accumulation of endogenous chemicals and by-products of normal metabolism that would otherwise be detoxified and excreted.

4) Vascular tumors.

In the two-year bioassay conducted in the CD1 mouse, a statistically significantly higher incidence of vascular tumors was noted in males at 1,000 and 8,000 ppm. In females, no statistically significant change in the incidence of vascular tumors was observed.

A search of the literature indicated there is very few chemical agents known to induce vascular tumors in humans, among them utherane and vinyl chloride were identified (Creech, J.L.Jr et Johnson, M.N. 1974). Angiosarcoma of liver in the manufacture of polyvinyl chloride. (J. Occup. Med. 16: 150-151; Marion, M.J., De Vivo, I., Smith, S., Luo, J.C. and Brandt-Rauf, P.W. 1996). The molecular epidemiology of occupational carcinogenesis in vinyl chloride exposed workers (Int. Arch. Occup. Environ. Health, 68: 394-398) and the mechanism underlying the formation of vascular tumors is through the formation of etheno-adducts, formed maybe by reactive oxygen species (Barbin, A. 2000. Etheno-adduct-forming chemicals: from mutagenicity testing to tumor mutation spectra. Mutation Res. 462: 55-69: Nair, J., Barbin, A., Velic, I. and Bartsch, H. 1998). Etheno DNA-base adducts from endogenous reactive species (Mutation Res. 424: 59-69). All those compounds would have been found to induce vascular tumors in the p53 model. Thus, the study using the genetically modified heterozygous p53 knockout mouse was designed to address the potential role of an indirect genotoxic mechanism in the induction of vascular tumors in mice.

Carbaryl was administered continuously via the diet to groups of 20 male heterozygous p53 knockout mice at concentrations of 0, 10, 30 100, 300, 1,000 and 4,000 ppm for at least 180 days. No treatment related tumors were found even in the highest dose ppm group. In particular, it should be noted that no tumors were found in the liver, kidney or vascular system. Under the conditions of this study, the NOEL is 4,000 ppm (approximately 716 mg/ kg b.w./day) for neoplastic changes.

C. Epidemiological/Worker Exposure Information

Epidemiological evaluations of carbaryl production workers, the population of exposed persons with the highest and most consistent carbaryl exposure, show no indication of effects on tumor incidence.

The two epidemiology studies of Aventis CropScience factory workers representing a sub-population of the general public with the highest exposure (i.e., exposure on a daily basis over many years). Thus, the data from these studies represent a potential "worst-case" for chronic carbaryl exposure to humans. The results from these studies show that

the overall mortality experience of the cohort is significantly less than expected when compared to both United States and West Virginia male death rates. In general, these studies support conclusion that there were no excess cases of cancer in this working population.

SUMMARY

Aventis CropScience strongly believes that the use of carbaryl products present no imminent carcinogenic risk to users based on the following points:

- Current data support a hypothesis that high doses of carbaryl in life-time studies produce tumors via a non-genotoxic mechanism, possibly related to altered metabolism at these high doses

- At doses less than the MTD, there was an increased incidence of tumors only in 1 site of 1 sex of 1 species.

- The increased incidence of vascular tumors in the male mice after two years of administration is of questionable biological significance

- In the p53 knockout mouse model, which was demonstrated, to be sensitive to the induction of vascular tumors by a genotoxic reference compound, carbaryl was found to be negative

- The weight-of-the evidence indicates that carbaryl shows little potential for genotoxicity

- Epidemiological data on carbaryl production workers show no increase in tumor incidence

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Part II - Dietary and Water Exposure/Risk Assessment

Line-by-Line Review of the Dietary and Water Exposure Assessment of the Human Health Risk Assessment Document for Carbaryl (June 19, 2001)

1.0 Executive Summary

Page:3 Paragraph:5 Line:3
EPA Comment:
No acceptable two-year reproduction study is available.

Aventis Response:
A study has been completed and submitted. The data gap to remove the 10X FQPA safety factor has been filled.

Page:6 Paragraph:2 Line:1
EPA Comment:
Monitoring data for carbaryl residues in ground and surface water are available but they are of limited utility in developing estimated environmental concentrations for the aggregate dietary (food and water) risk assessment.

Aventis Response:
Monitoring data submitted by Aventis is directly applicable to drinking water residue use in the aggregate (food and water) assessment. Worst-case community water supply systems, targeted for maximum carbaryl use, were monitored for three years on a weekly basis during peak carbaryl use times.

4.0 Exposure Assessment and Characterization

4.2.1 Residue Profile

Page:25 Paragraph:2 Line:1
EPA Comment:
HED conducts dietary risk assessments using the DEEM™ which incorporated consumption data generated in USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1989-1992.

Aventis Response:
The CSFII data for the years 1994-1996 have been available for several years now. These data should be used as it reflects the most recent eating patterns and habits of the U.S. population that is currently available.

Page:26 Paragraph:3 Lines:1-5

EPA Comment:

Most of the processing factors were obtained from processing studies submitted by the registrant and compiled in a memo entitled "Carbaryl Anticipated Residues for Carcinogenic Dietary Risk Assessment." S. Hummel, 12/3/93.

Aventis Response:

The studies in this memo are older processing studies submitted in the 1980's or even earlier. New residue processing studies were done in the early- to mid-nineties in conjunction with the Residue Chemistry DCI. These studies are listed with MRID numbers in EPA's Product and Residue Chemistry documents. The factors are listed in the 'Discussion *S*ection*' below.* These factors should be used in the dietary risk assessment as they represent newer, GLP data.

Page:27 Paragraph:1 Line:5

EPA Comment:

As discussed in section 3.2, the 10X safety factor is retained for carbaryl.

Aventis Response:

The data gaps and concerns for the FQPA safety factor have been addressed by Aventis with the submission of the 2-generation rat reproduction study and the additional data generated for the developmental neurotoxicity study. Based upon the outcome of the studies provided, the 10X safety factor is no longer justified and should be removed. There are no populations of concern in this assessment when the corrected RfD is used in the risk calculation (excluding poultry and using the CMBS data).

4.2.2 Acute Dietary Exposure Assessment

Page:29 Table 6:

EPA Comment:

The top heading of the table is labeled "Acute-All Commodities at the 99.9th percentile of exposure (Market Basket Survey Data Used **in Place** of PDP/FDA data.)

Aventis Response:

This top table heading should be labeled: "Acute-All Commodities at the 99.9th Percentile of Exposure (Market Basket Survey Data **Not Included**).

4.2.5 Characterization/Uncertainties of the Risk Estimates

Page:31 Paragraph:1 Line:1

EPA Comment:

Cooking factors were available for potatoes only.

Aventis Response:

A survey of the literature data revealed numerous cooking and washing studies for carbaryl. See '*Discussion S*ection' for a list of these studies and a table of processing/washing/cooking factors that can be derived for carbaryl from these literature studies.

4.3 Water Exposure/Risk Pathway

Page: 31 Paragraph: 5 Line: 4

EPA comment:

Some non-targeted monitoring data are available but they are of limited utility in developing estimated environmental concentrations (EECs) for ecological and human health risk assessment.

Aventis' response:

Aventis believes that the highest estimated EECs of relevance for ecological risk assessment are not relevant for estimating human health risks due to the lack of proximity of drinking water sources to likely areas of highest ecological risk. The drinking water monitoring program conducted by the registrant provides a real world assessment of the potential for human exposure to carbaryl in drinking water derived from surface water. Drinking water concentrations derived from PRZM/EXAMS greatly overestimate the potential exposure to carbaryl in drinking water, generally by several orders of magnitude.

Monitoring Data

Page: 32 Paragraph: 4 Line: 2 (and elsewhere)

EPA comment:

USGS NAQWA (sic) program

Aventis' response:

The correct abbreviation for the USGS water monitoring program is NA**WQ**A.

Page: 32 Paragraph: 5 Line: 2

EPA comment:

Because of limitation in the analytical methods used there is some question as to the accuracy of carbaryl analysis.

Aventis' response:

This generalized statement needs to be qualified or deleted. Whereas the authors of reports written as part of the NAWQA program have been clear about the potential limitations of the quantitative nature of the carbaryl data in the database, they have also been clear about the validity of the qualitative nature of the data. The use of the multi-residue method in the NAWQA program does have some limitations as a result of the large numbers of diverse pesticides and degradation products that they are monitoring. However, the QC/QA data generated as part of the NAWQA program (described in the discussion section on surface water at the end of the EFED response) demonstrates the validity of the detections of carbaryl in the studies. The monitoring study conducted by the registrant, and reported in this section, does not have the same potential limitations in the analytical method since the method is looking specifically for only carbaryl. Therefore, the analytical method used by the registrant does not raise questions about the accuracy of the carbaryl analysis.

Page: 32 Paragraph: 5 Line: 3

EPA comment:

Poor analytical methods probably have resulted in lower detection rates and lower concentrations than actually present.

Aventis' response:

This generalized statement should be deleted for reasons provided above and in the discussion section of the EFED response.

Page: 33 Paragraph: 2 Line: 6

EPA comment:

The data do not give a good indication of the effectiveness of treatment because samples existing and entering the treatment plant were different. In several cases, finished water had higher concentrations than raw water and finished water had detectable carbaryl when the raw did not.

Aventis' response:

Obtaining matched samples is not possible because of varying residence time through the treatment system, as well as mixing that occurs. The minimal amount of carbaryl residues found also made observations regarding treatment less definitive. However, an examination of the data does indicate that carbaryl concentrations were generally lower in finished water than in raw water samples collected at the same time. These data do include several instances where carbaryl was detected over a few weeks in the raw water so the effect of sample time is less important. The statement regarding several cases of finished water having higher concentrations than raw water is misleading and certainly does not consider the analytical uncertainty for concentrations below the level of quantification and near the level of detection. There were only two cases when finished water was greater than raw water when the concentrations in finished water were greater than 0.01 ppb (only one-third of the quantification limit). One

case was when the raw water was 0.009 ppb and the finished water was 0.011 ppb. These two analyses are essentially equivalent, especially considering that they are only about a third of the quantification limit. The other case was at the Deerfield community water system. This drinking water facility uses a small river without a reservoir as a source for a small Community Water System. Farms are located immediately upstream of the facility. The intake is also not continuous (shut down over weekends). Therefore, getting a matching sample is quite difficult, especially for a short duration spike as a result of spray drift, summer thunderstorm, or perhaps a spill that almost immediately enters the river as a runoff event. The rarity of this event is demonstrated by the absence of residues of this magnitude the next year (2000). Samples collected through this time of the year in 2001 also do not indicate a similar event. Although the data from this site cannot be used to determine the peak concentration, the data provide a distribution of residues through the three-year period which will define up to the 99th percentile concentration of the distribution.

The Deerfield, Michigan community water system is one of the systems in which the greatest variability of residues would be expected. Most of the other community water systems are located on larger rivers, lakes, or reservoirs.

Because the design of study called for analysis of finished water only when there were residues in the raw water, there was only one finished sample analyzed when the raw water contained no residues. This sample was collected at the Deerfield community water system at the sampling interval after the finding of 0.16 ppb in the Deerfield system. The residue level in this sample was 0.004 ppb. The difference between 0.004 ppb and non-detect is insignificant, and if real can probably be attributed to water at much higher concentrations remaining in the system from the previous week.

Page: 33 Paragraph: 2 Line: 10

EPA comment:

This illustrates that carbaryl contamination is transient, and that it is unlikely that any sampling would catch the actual peak concentration

Aventis' response:

The role of a peak concentration is in dietary exposure assessment is undergoing re-examination within EPA. The current policy of EPA appears to define a certain percentile as an appropriate value for use in screening assessments, but the exact percentile to be used is being defined by EPA management. For more comprehensive assessments, a distribution of values is preferred.

The peak concentration in this study was measured at a community water system on a small river. The registrant agrees that the sampling schedule was not adequate to determine the true peak in such systems. Most of the other community water systems are located on larger rivers, lakes, or reservoirs. Therefore, the peak values are not likely to be an order of magnitude greater than

the amounts detected in this monitoring program.

Page: 33 Paragraph: 2 Line: 13

EPA comment:

Non-targeted monitoring, such as the NAWQA program has shown that much higher concentrations occur.

Aventis' response:

The main reason why the drinking water monitoring study did not show residues as high as in the NAWQA program is the location of the sampling points. Drinking water supplies tend to be located on larger surface water bodies than NAWQA sampling points (or in other words, the intakes for community water systems tend to be downstream of NAWQA sampling points). This additional time allows for additional degradation and dilution to occur. Finding the highest concentration at the Deerfield, Michigan system is not surprising since this intake is on one of the smallest surface water bodies included in the monitoring study.

Page: 33 Paragraph: 2 Line: 14

EPA comment:

This study, while useful, does not provide sufficient information to allow estimation of actual peak and mean concentrations that actually occur in all areas or the effect of treatment.

Aventis' response:

Because most of the samples did not contain carbaryl residues, accurate estimates of the actual peak and mean concentrations can not be obtained. However, the distributions obtained from all sites can be used to define up to the 99thpercentile concentration. The average cannot be accurately determined; however, the time-weighted average is only slightly above the limit of detection (and certainly less than 0.01 ppb) at all 20 sites. The study provides information on concentrations of carbaryl in community water systems most likely to contain the highest concentrations of carbaryl. Residues of carbaryl in other areas would be expected to be lower. The study does not provide information on concentrations in smaller surface water bodies or in areas where surface water is not used for drinking water. Because drinking water concentrations are what is needed for FQPA dietary calculations, this information is suitable for use in dietary exposure assessments.

Page: 34 Table 8

EPA comment:

Carbaryl EEC Values

Aventis' response:

Aventis has provided a more detailed response to this same table that is presented as Table 6 in the draft EFED chapter. An electronic copy of the EPA Memorandum on “Refined Estimated Environmental Concentrations for

Carbaryl" (DP Bar Code D267276, authored by E. Laurence Libelo, July 23, 2001, and sent to Anthony E. Britten and Virginia Dobozy) was provided to Aventis and contains the PRZM model inputs that were used to generate the EECs shown in this table. An abbreviated version of our response to the information from EFED is included below.

It would be useful to add another column to Table 8 to specify which method of application was used to generate the EECs. It would also be of benefit for the Agency to state which of the carbaryl labels were used to develop the "maximum" label application rate scenarios.

The model parameters listed in the Memorandum show that the "average" scenarios for citrus and apples were conducted using aerial applications. Few applications to these crops are made aerially. Therefore, the model results over-estimate the contributions from spray drift since the "average" applications to these crops are made using ground airblast equipment with lower spray drift inputs.

The "maximum label rate" application scenario for apples that is allowed by the Sevin brand XLR PLUS label (E.P.A. Reg. No 264-333), the Sevin brand 80WSP and CHIPCO Sevin brand 80WSP labels (E.P.A. Reg. No 264-526) and the CHIPCO Sevin brand SL label (E.P.A. Reg. No 264-335) is 5 applications at 3-lb. ai/A/application made every 14 days. The scenario used in the model applies less than the maximum amount of product allowed by the labels. In addition, application timing was used in the modeling for the Index Reservoir scenario (applications made by air every 4 days) that would be a violation of the Aventis labels that restrict applications to a minimum of every 14 days.

The "average" scenario for sweet corn in Ohio should be 3 applications at 1.1 lb ai/A/application (as noted in the memo, "Average application rate from Quantitative Usage Analysis for Carbaryl, prepared July 21, 1998 by Frank Hernandez, OPP/BEAD") and not the 2 applications at 3.4 lb ai/A/application as listed in the table. The PRZM input file shows the correct inputs of 3 applications at 1.1-lb ai/A/application. Likewise, the "average" scenario for sugar beets in Minnesota should be 1 application at 1.3-lb ai/A/application. The "Citrus" scenario would be more appropriately labeled Oranges. For the average scenario, the 3.4 lb. ai/A/application rate listed in Table 8 is for oranges which is the highest "average" application rate for any type of citrus. Therefore, this "average" scenario for oranges is at the high end for all citrus and overestimates the EECs for use in the other citrus crops.

4.3.1 DWLOCs for Acute Dietary Exposure.

Page:35 Paragraph:1 Line:7

EPA Comment:

Therefore, there is no allowable contribution for water to the risk cup.

Aventis Response:

Based on a corrected acute reference dose for carbaryl (no 10X FQPA safety factor) and the exposure assessment that uses the Carbamate Market Basket Data, DWLOCs can be calculated. (see 'Discussion Section' for calculations.)

4.3.2 DWLOCs for Chronic Dietary Exposure

Page 36 Table 9

EPA Comment:

DWLOC(chronic) calculations in Table.

Aventis Response:

Based on a corrected chronic reference dose for carbaryl (no 10X FQPA safety factor) the DWLOCs should be calculated as shown in the 'Discussion Section'. Based on the corrected values, there are no population subgroups of concern.

8.0 Data Needs/Label Requirements

Product Chemistry Data Gaps

Page:97 Paragraph:2 Line 1

EPA Comment:

Additional data are required depicting carbaryl residue in/on cotton gin byproducts.

Aventis Response:

Aventis is not supporting the cotton use and has removed this crop from the labels. Aventis CropScience requested cancellation of this use in a letter to Mr. George Tompkins, RD, on January 22, 1999. A Federal Register Notice dated April 14, 1999 announced receipt by the Agency of an application from Rhone-Poulenc Ag Company (now Aventis CropScience) to cancel the use of carbaryl products on cotton

Line-by-Line Review of the Supporting Document "Revised Dietary Exposure Analysis for the HED Revised Human Health Risk Assessment (Felicia A. Fort; April 26, 2001)"

Conclusions/Summary

Page:2 Paragraph:1 Line:8
EPA comment:

At the present time, information from the industry-sponsored Carbamate Market Basket Survey has not been completely approved for use in dietary risk assessments.

Aventis Response:

The CMBS protocols were presented to EPA for comment before the studies were started. These studies were specifically conducted to obtain more realistic residues for consumer's "at the plate" to be used in dietary assessments. As agreed with EPA before this study was started, the CMBS data should take precedence over others for use in dietary assessment (after their quality review has been completed).

Chronic

Page:2 Paragraph:2 Line:8
EPA comment:

When poultry is not considered in the risk estimate, the dietary exposure is $\leq$ 6% of the cPAD for all population subgroups.

Aventis Response:

When a corrected cRfD is used (no FQPA 10X) and poultry is not included in the risk estimate, the dietary exposure is $\leq$ 0.6% of the cRfD for all population subgroups.

Acute

Page:3 Continuation from Paragraph:4 of Page 2 Line:3
EPA Comment:

Subsequent dietary analyses and all additional sensitivity analyses were conducted without poultry; the risk estimates were still of concern for all population subgroups with the all infants population subgroup consuming 260% of the aPAD when CMBS data were used.

Aventis Response:

When a corrected aRfD is used (no FQPA 10X) , there are no concerns for all population subgroups. The all infants population subgroup consumes 26% of the aRfD when CMBS data are used.

Residue Data

Page: 5; Paragraph: 2; Line: 4
EPA comment:

FDA monitoring data were used for … cherries, raspberry, blueberry, raspberry, asparagus, …

Aventis response:

Second listing of "raspberry" can be deleted.

Page: 5; Paragraph: 2; Line: 9
EPA comment:

Field trial data were used for the commodities, garden beets, turnips, mustards, dried beans, almonds, pecans, walnuts, field corn grain, rice, flax seed, okra, olive, peanuts, pistachio, and sunflower.

Aventis response:

According to Table 6a, the following commodities should be added to this list: sugar beets and dried peas

Page: 5; Paragraph: 2; Line: 11
EPA comment:

For oysters, the tolerance of 2 ppm was used in the assessment.

Aventis response:

According to Table 6a, the tolerance of 0.2 ppm was also used for Dill (fresh) in the assessment.

Processing Factors

Page 6 Paragraph:1 Table 2
EPA comment:

Most of the carbaryl processing factors were obtained from processing studies submitted by the registrant and compiled in a memo entitled "Carbaryl Anticipated Residues for Carcinogenic Dietary Risk Assessment", S. Hummel, 12/3/93.

Aventis Response:

As previously state, the studies in this memo were older processing studies submitted in the 1980's or even earlier. New residue processing studies were done in the early- to mid-nineties in conjunction with the Residue Chemistry DCI. These studies are listed with MRID numbers in EPA's Product and Residue Chemistry documents. The factors are listed in the Discussion section. These factors should be used in the dietary risk assessment as they represent newer, GLP data.

Consumption data

Page:7 Paragraph:1 Line:1

EPA Comment:

HED conducts dietary risk assessments using the DEEM™ which incorporated consumption data generated in USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1989-1992.

Aventis response:

As previously stated the CSFII data for the years 1994-1996 have been available for several years now. These data should be used as it reflects the most recent eating patterns and habits of the U.S. population that is currently available.

Results

Page:7 Paragraph:2 Line 2

EPA comment:

Additional cooking and processing studies would allow further refinement.

Aventis response:

A literature search resulted in many literature references to cooking, washing and peeling studies for carbaryl treated commodities. Average cooking, washing factors can be derived from these literature studies. See the 'Discussion Section' for a list of the references and the average calculated factors.

Characterization/Uncertainties of the Risk Estimates.

Page:9 Paragraph: 2 Line:1

EPA comment:

Additional cooking factors could further reduce the risk estimates.

Aventis response:

Numerous literature studies have been conducted on other commodities, see the 'Discussion Section'.

Attachment 1: Anticipated Residues Summary and Residue Distribution Files

Table 6a: Summary of Anticipated Residues for Carbaryl (Market Basket Data not included) and Table 6b: Summary of Market Basket Survey Data.

Aventis Comments:

EPA/BEAD reports a maximum of 84% crop treated for cranberries and an average of 39% crop treated for cranberries. Three years of data were obtained from the Cranberry Institute (memo from Gary Deziel, Manager of Research and Communication, Cranberry Institute.) These data show maximum acres treated

for 1992, 39%; 1996, 37%; and 1998, 36%. Based on these data and private conversations, the maximum percent crop treated for cranberries is 39% with an average of 37%.

Barley, oats, rye and cotton/cottonseed are not supported by Aventis and should not be included in the risk assessment. A letter date May 7, 1999 to Ms. Kathryn Boyle confirmed Rhône-Poulenc's (now Aventis CropScience) decision not to support the registration of carbaryl products on the commodities barley, oats, and rye. These uses have been deleted from our technical and end-use product labels.

Residue Data Sources: The following data sources are more appropriate to use for the crops listed in the table, according to priority rules for use of residue data (Market Basket (MBS)>PDP>FDA>Field Trial (FT)>tolerance) and the Translation of Monitoring Data HED SOP 99.3 (March 26, 1999).

Food	**EPA Used**	**More Appropriate Source**
Brussels Sprouts	Cabbage FDA	Lettuce MBS
Cabbage	Cabbage FDA	Lettuce MBS
Collards	Mustard FT	Spinach PDP
Eggplant	Pepper FDA	Tomato MBS
Endive	Leaf lettuce FDA	Spinach PDP
Kale	Mustard FT	Spinach PDP
Kohlrabi	Cabbage FDA	Broccoli MBS
Mustard Greens	Mustard FT	Spinach PDP
Paprika	H. Pepper FDA	Tomato MBS
Chili Pepper	H. Pepper FDA	Tomato MBS
Other Pepper	H. Pepper FDA	Tomato MBS
Sweet Pepper	S. Pepper FDA	Tomato MBS
Pimentos	H. Pepper FDA	Tomato MBS
Strawberries	Strawberry FDA	Strawberry PDP
Strawb. Juice	Strawberry FDA	Strawberry PDP
Swiss Chard	Celery PDP	Spinach PDP

Page 41 Residue Distribution Files

RDF#68 Almonds and RDF#69 Chestnuts appear to have used the almond hull field trial data rather than the almond nutmeat field trial (mostly NDs) data for the residue values.

Page 44 Residue Distribution Files

RDF#86 to RDF#92. Meat and milk. There is no clear indication or discussion anywhere in the document regarding the source of these residue data or how the values were derived (e.g., derived from theoretical animal diets or monitoring data). (see Discussion below).

Part II - Dietary and Water Exposure/Risk Assessment

SUPPORTING DISCUSSIONS

Surface Water Concentrations

In section 5.0, page 33 (Table 6), EPA has based its assumptions about concentrations of carbaryl in drinking water upon model simulations. The data from the registrant drinking water monitoring program provide the best estimate of concentrations of carbaryl in drinking water. This study uses the sampling design for acute endpoints recommended in industry/EPA meetings during 1999 (weekly sampling during times of peak concentrations over a three-year period). Twenty sites representing the highest carbaryl use areas were selected based on the information provided in Appendix I. Included are 16 sites in agricultural areas and 4 locations in urban areas. Samples were collected from the inlet and outlet water at each sampling interval. Outlet samples were only analyzed when residues were present in the inlet samples. The analytical method had a limit of quantification of 0.030 ppb and a limit of detection of 0.002 ppb.

Error! Reference source not found. summarizes the results of the monitoring at each of the 20 community water systems. The maximum concentration observed was 0.16 ppb (average of four samples, the highest was 0.18 ppb) in a finished water sample from the Deerfield community water system located on the River Raisin in Lenawee County, Michigan. There were only five other samples above the limit of quantification of 0.030 ppb. One was a raw water sample containing 0.31 ppb from the Little Potato Slough Mutual community water system near Lodi in San Joaquin County, California (the source is the Little Potato Slough). The corresponding finished water sample was 0.007 ppb. A second one was a raw water sample in Brockton, MA which contained 0.031 ppb. No detectable residues were found in the corresponding finish water sample. The last three samples were from the Shades Mountain plant of the Birmingham community water system on the Cahaba River in Jefferson County, Alabama . Two were raw and finished samples of 0.038 and 0.032 ppb at the same sampling interval in 2001. The other sample was 0.035 ppb in the raw water in a 2000 sample (the corresponding finished sample did not contain carbaryl residues. All residues were transient so the time weighted average concentration of carbaryl in each of the years was 0.005 ppb or less at all 20 community water systems.

Table 1. Summary of results from the carbaryl drinking water monitoring study.

Site	Major Uses	Maximum Concentration (ppt)						TWA Conc. (ppt)* in Outlet Water	
		Inlet Water			Outlet Water				
		1999	2000	2001**	1999	2000	2001**	1999	2000
Manatee, FL	citrus	9	3	ND	11	ND	NA	1	1
West Sacramento, CA	orchards, nuts	3	24	ND	3	10	NA	1	1
Lodi, CA	orchards, nuts	12	31	ND	4	7	NA	1	1
Riverside, CA	grapes, tree crops	8	ND	ND	ND	NA	NA	1	1
Lake Elsinore, CA	citrus	ND	3	6	NA	NA	Analysis Pending	1	1
Corona, CA	citrus	ND	ND	ND	NA	NA	NA	1	1
Beaumont, TX	various agricultural	ND	ND	ND	NA	NA	NA	1	1
Point Comfort, TX	rice, tree crops	18	5	ND	ND	ND	NA	1	1
Penn Yan, NY	grapes, apples	ND	23	ND	NA	ND	NA	1	1
Westfield, NY	grapes, apples	21	5	ND	ND	9	NA	1	1
Jefferson, OR	vegetables, strawberries	ND	10	ND	NA	ND	NA	1	1
Coweta, OK	pecans	4	ND	***	ND	NA	***	1	1
Pasco, WA	apples, potatoes	2	3	ND	ND	ND	NA	1	1
Manson, WA	apples	ND	ND	ND	NA	NA	NA	1	1
Deerfield, MI	vegetables	10	4	ND	160	ND	NA	5	1
Brockton, MA	cranberries	31	27	ND	ND	3	NA	1	1
East Point, GA	home and garden	18	18	4	3	8	ND	1	1
Midlothian, TX	home and garden	14	ND	14	ND	NA	ND	1	1
Cary, NC	home and garden	4	ND	ND	ND	NA	NA	1	1
Birmingham, AL	home and garden	23	35	38	ND	ND	32	1	1

* Annual Time Weighted Concentration, outlet values substituted for inlet values when available; values below the detection limit were considered to be half the detection limit.

** Results represent one to six months of sampling into the third year program.

*** No results available for the third year of sampling.

ND Not detected.
NA No outlet samples analyzed due to carbaryl residues not being detected in inlet samples.

Appropriateness of the Carbamate Market Basket Survey Data

The Agency questions the appropriateness of the use of these data in several discussions of the dietary risk assessment. The CMBS Task Force met with EPA/HED before the start of the study to review the purpose of the study and protocols for the study. The EPA assured the task force that the study data would be used in risk assessments, taking precedence over all other monitoring or field trial data available for those crops. A surrogation plan according to HED SOP 99.3 was also assured. The specific target of this study was to measure more realistic residues that consumer's are exposed to "at the plate". The study protocol was designed to mimic the typical consumer shopping at his/her local grocery store and the preparation he would do at home before consuming or further cooking/preparing the food. The PDP data is taken from distribution centers before the grocery stores are reached and some typical preparation is done. The CMBS data would therefore be expected to have somewhat lower and more realistic measures of residues consumers are exposed to. There is likely to be even further reduction of residues before the food is "put on the plate" by storing, cooking, slicing, peeling or other preparation. It would be very difficult to justify within the industry, further generation of these much needed data for other crops/compounds if EPA decided at this late date that the data could not be used.

Secondary Residues

Although residue distribution files are presented by the Agency in Attachment 1 of the Dietary Assessment Support Document for meat and milk commodities, there is no place in the document where these residue numbers and residue distribution files are discussed. Aventis neither can determine the source of the residue data was (monitoring or theoretical animal diets) nor how the data were translated or calculated. We request that a more detailed description of this process be provided to us.

Processing Factors

EPA uses processing factors listed in a 1993 memo by S. Hummel. Examination of this document shows that the source of these processing factors is studies that were conducted in the 1980s or even earlier. As part of the Residue Chemistry DCI for carbaryl in the early 1990s, numerous residue-processing studies were conducted along with residue (RAC) field trials. These studies are referenced in the Product and Residue Chemistry Support Document prepared by the EPA. These processing studies and the derived factors, which were conducted under GLP conditions to more recent specifications, are the factors that should be used in the current dietary risk assessment. A table of these factors is listed here.

Food	Process	Average PF
Citrus	Dried Pulp	1.46
	Juice	0.06
	Oil	13.92
Molasses		0.47
Field Corn	Small grits	0.25
	Meal	0.25
	Flour	0.25
	Starch	0.25
	Crude Oil	3.38
	Refined Oil	0.25
Grapes	Pasteurized Juice	0.24
	Wet Pomace	1.37
	Dry Pomace	3.85
	Processed Raisins	1.37
	Unprocessed Raisins	2.17
	Raisin Waste	4.88
Olives	Olive oil	0.81
Peanuts	Meal	0.29
	Refined Oil	0.29
Pome	Juice	0.40
	Wet Pomace	1.26
	Dry Pomace	3.70
Potatoes	Wet Peel	1.00
	Dry Peel	0.75
	Flakes	0.75
	Chips	0.75
Rice	Polished Rice	0.03
	Hulls	2.37
	Bran	0.36
Soybeans	Hulls	0.35
	Meal	0.22
	Crude Oil	2.71
	Refined Oil	0.005
Sunflowers	Hulls	0.35
	Meal	0.03
	Crude Oil	0.18
	Refined Oil	0.03
Tomatoes	Juice	0.52
	Wet Pomace	1.74
	Dry Pomace	2.89
	Puree	1.26
	Paste	2.01
Wheat	Middlings	0.42
	Shorts	0.83
	Asp Grain Fractions	11.79
	LG Flour	0.08
	Patent Flour	0.10
	Wheat Germ	0.65
	Wheat Bran	1.03

Cooking Washing Factors

EPA states several times that cooking/washing studies would further reduce the anticipated residues used in the assessment and reduce the risk estimates. Aventis conducted a general literature search for studies such as this. A table of factors is listed followed by the references found in the general literature. Average cooking, washing and canning factors could be derived from these references and applied to the risk assessment as supported by these literature studies.

Food	Process	Reduction	Reference
Broccoli	Cooking/washing	55%	8
Cabbage Heads	Cooking	90%	2
Cabbage Heads	Washing	75%	2
Cauliflower	Cooking/washing	94%	4
Grapes	Washing	49%; 85%	7
Green Beans	Canning	100%	11
Green Beans	Cooking/blanching	81%	11
Green Beans	Washing	52%	11
Okra	Cooking	42%; 25%	1,14
Okra	Cooking/steaming	82%	1,14
Okra	Washing	80%;66%;70%	1,14
Onions	Washing	89%;98%;100%	9
Orchard Fruit	Washing	50%	12
Peas	Cooking/boiling	85%	3
Peas	Washing	70%	3
Spinach	Canning	99.5%	10
Spinach	Washing	70%	10
Tomatoes	Peeling/washing	99%	5,6
Tomatoes	Puree/catsup	98%	5,6
Tomatoes	Washing	66%; 68%, 84%	5,6

1. Indian Journal of Plant Protection. 1996, 24, 86-89.
2. Pest Management and Econ. Zoology. 1994, 2, 131-134.
3. Plant Protection Bulletin. 1988, 40, 12-13.
4. Beitrage zur Trop. Land. Veter. 1982, 20, 89-95.
5. Indian Journal of Entomology. 1978, 40, 187-190.
6. Indian Journal of Entomology. 1973, 34, 31-34.
7. Indian Journal of Ag Sciences. 1978, 48, 179-183.
8. J. Ag. Food Chem. 1969, 15, 215-216.
9. J. Food Science Technology. 1978, 15, 215-216.
10. J. Ag. Food Chem. 1968, 16, 967-973.
11. J. Ag. Food Chem. 1968, 16, 962-966.
12. J. Assoc. Off. Anal. Che,. 1989, 72, 533-535.
13. Env. Health Criteria 1994, 153, 358pp.

14. Indian Journal of Ag Sciences. 1976, 45, 139-144.
15. Indian Journal of Env. Health

Acute DWLOC

EPA indicates there is no room in the risk cup for water and DWLOCs cannot be calculated. If a corrected acute RfD is used (no FQPA 10X), acute DWLOCs can be calculated as follows:

US Population:
Acute RfD= 0.03 mg/kg
Exposure=0.005937 mg/kg (from EPA assessment without poultry and with CMBS data)
70 kg. Man, 2-liter consumption
Acute DWLOC is 842ppb

Children 1-6:
Acute RfD=0.03 mg/kg
Exposure=0.008363 mg/kg (from EPA assessment without poultry and with CMBS data)
10kg child, 1 liter consumption
Acute DWLOC is 216ppb

Aventis monitoring programs of raw surface drinking water have shown 0.16 ppb as the maximum encountered. NAWQA data shows 5 ppb as the maximum encountered in ground or surface water. These monitoring numbers would indicate there is no concern for dietary and drinking water exposure in an aggregate situation.

Chronic DWLOCs

EPA indicates there is some concern for subpopulations for drinking water in the chronic scenarios. If a corrected chronic RfD is used (no FQPA 10X) chronic DWLOCs can be calculated as follows:

US Population:
Chronic RfD=0.01 mg/kg
Exposure = 0.000037 mg/kg (from EPA assessment without poultry)
70kg man, 2 liter consumption
Chronic DWLOC is 349 ppb

Children 1-6:
Chronic RfD=0.01 mg/kg
Exposure=0.000062 mg/kg (from EPA assessment without poultry)
10kg child, 1 liter consumption
Chronic DWLOC is 99 ppb

Aventis and NAWQA monitoring data averages are significantly less than the maximum values of 0.16 ppb and 5 ppb numbers cited above. There are no populations of concern for aggregate exposure to food and water for carbaryl.

Part III - Residue Chemistry Considerations

Line-by-Line Review of the Residue Chemistry Information Included in the Human Health Risk Assessment Document for Carbaryl (June 19, 2001)

1.08 Data Needs/Label Requirements

Product Chemistry Data Gaps

Page 95 Paragraph 3 Line 1-3

EPA comment:

A review of the labels and supporting residue data indicate that several label amendments are required. Details are provided in the Product and Residue Chemistry Chapters (DP Barcode: D238151) dated October 17, 2000.

Aventis response:

Most of these label amendments have already been made and approved by the EPA. See detailed information in the review of the Residue Chemistry Chapter below.

Page 96 Paragraph 7 Lines 1-2

EPA comment:

Adequate residue data are available on olives provided that use directions for olives are amended to remove the statement allowing the use of summer oil as an adjuvant.

Aventis response:

The statement allowing the use of summer oil as an adjuvant has already been deleted from the use directions for olives.

Page:97 Paragraph:2 Line 1

EPA comment:

Additional data are required depicting carbaryl residue in/on cotton gin byproducts.

Aventis response:

Aventis is not supporting the cotton use and has removed this crop from the labels. Aventis CropScience requested cancellation of this use in a letter to Mr. George Tompkins, RD, on January 22, 1999. A Federal Register Notice dated April 14, 1999 announced receipt by the Agency of an application from Rhone-Poulenc Ag Company (now Aventis CropScience) to cancel the use of carbaryl products on cotton.

Page:97 Paragraph:3 Lines 1-4

EPA comment:

The registrant does not intend to support carbaryl on avocados, barley, maple sap, oats, rye, and sweet sorghum; however, IR-4 has indicated (correspondence from K. Dorschner, IR-4 Project, 9/15/94) that they may fulfill the residue data requirements for some of these commodities. These data have not been submitted.

Aventis response:

IR-4 has not generated the residue data necessary to support these uses. Aventis CropScience will not support these uses.

Page:97 Paragraph:4 Lines 1-2

EPA comment:

The reregistration requirements for magnitude of the residue in livestock commodities are not fulfilled. Additional data are required to support dermal and poultry house uses.

Aventis response:

Aventis CropScience will neither support dermal nor poultry house uses of carbaryl. A request for cancellation of these uses in accordance with section 6(f)(1) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) will be submitted shortly to the Agency.

Line-by-Line Review of the Supporting Document "Product and Residue Chemistry Chapters for the Reregistration Eligibility Decision (Felecia Fort; November 14, 2000)"

Cover Memo
Residue Chemistry

Page 2 Paragraph 3 1st Bullet Pont

EPA comment:

A review of the labels and supporting residue data indicate that several label amendments are required.

Aventis response:

Most of these label amendments have already been made and approved by the EPA.

Page 3 6th Bullet Point Lines 1-2

EPA comment:

Adequate residue data are available on olives provided that use directions for olives are amended to remove the statement allowing the use of summer oil as an adjuvant.

Aventis response:

The statement allowing the use of summer oil as an adjuvant has already been deleted from the use directions for olives.

Page:4 1st Bullet Point Line 1

EPA comment:

Additional data are required depicting carbaryl residue in/on cotton gin byproducts.

Aventis response:

Aventis is not supporting the cotton use and has removed this crop from the labels. Aventis CropScience requested cancellation of this use in a letter to Mr. George Tompkins, RD, on January 22, 1999. A Federal Register Notice dated April 14, 1999 announced receipt by the Agency of an application from Rhone-Poulenc Ag Company (now Aventis CropScience) to cancel the use of carbaryl products on cotton.

Page:4 2nd Bullet Point Lines 1-4

EPA comment:

The registrant does not intend to support carbaryl on avocados, barley, maple sap, oats, rye, and sweet sorghum; however, IR-4 has indicated (Correspondence from K. Dorschner, IR-4 Project, 9/15/94) that they may fulfill the residue data requirements for some of these commodities. These data have not been submitted.

Aventis response:

IR-4 has not generated the residue data necessary to support these uses. Aventis CropScience will not support these uses.

Page:4 3rd Bullet Point Lines 1-2

EPA comment:

The reregistration requirements for magnitude of the residue in livestock commodities are not fulfilled. Additional data are required to support dermal and poultry house uses.

Aventis response:

Aventis CropScience will neither support dermal nor poultry house uses of carbaryl. A request for cancellation of these uses in accordance with section 6(f)(1) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) will be submitted shortly to the Agency.

Residue Chemistry Chapter of the Reregistration Eligibility Decision (RED) Document

Residue Chemistry Considerations

Summary of Science Findings

Page 3 Table A1. Carbaryl EPs with Food/Feed Uses Registered to Aventis Ag Company

EPA comment:

Label acceptance dates for Carbaryl EPs are listed

Aventis response:

Label acceptance dates listed for certain products are incorrect. Acceptance dates of the most recently EPA approved labels for SEVIN® 80S, SEVIN® 5% Bait, SEVIN® XLR PLUS, SEVIN® RP2, SEVIN® RP4, SEVIN® 4F, and SEVIN® 80WSP are listed below.

EPA Reg. No.	Corrected Label Acceptance Date	Product Name
264-316	1/13/2000 Notification 7/26/2001	SEVIN® brand 80S Carbaryl Insecticide
264-320	6/11/1999	SEVIN® brand 5% Bait Carbaryl Insecticide
264-333	2/8/2001	SEVIN® brand XLR Carbaryl Insecticide (Alternate brand name: SEVIN® brand XLR PLUS Carbaryl Insecticide)
264-334	Notification 10/29/1999	SEVIN® brand RP2 Carbaryl Insecticide
264-335	10/18/2000	SEVIN® brand RP4 Carbaryl Insecticide
264-349	1/13/2000	SEVIN® brand 4F Carbaryl Insecticide

264-526	4/12/2000	SEVIN® brand 80 WSP Carbaryl Insecticide

The following SLN Nos are no longer active:

SEVIN® brand 50W: CA830007, NC820007
SEVIN® brand 80S: CA8300007, WA900013
SEVIN® brand XLR: NC960003, OH960003, OR950006, PA960002, VA950001, WA940021
SEVIN® brand 4F: FL890037

Page 3 Paragraph 2 Lines 1-2

EPA comment:

Use directions for sugar beets on all labels should be amended to specify a maximum of two applications at a maximum single application rate of 1.5-lb ai/A and a 28-day PHI.

Aventis response:

This change has been made on all Aventis CropScience product labels.

Page 3 Paragraph 3 Lines 1-2

EPA comment:

Use directions for sweet corn on the G formulations should be amended to specify a 48-day PHI for stover.

Aventis response:

This change has been made.

Page 3 Paragraph 4 Lines 1-2

EPA comment:

As the registrant is no longer supporting uses on avocado, the SLN labeling (CA83007) for use of carbary (sic) on avocados in CA should be revoked.

Aventis response:

This SLN label has been canceled.

Page 3 Paragraph 5 Line 1

EPA comment:

Use directions for cotton on all labels should be amended to remove the 14-day PHI for forage.

Aventis response:

The use of carbaryl products on cotton has been canceled.

Page 4 Paragraph 1 Lines 1-3

EPA comment:

Based on acceptable residue data on okra from IR-4, the registrant should amend use directions on FIC and WP labels to specify a maximum or four applications per season at 1.5 lb ai/A/application at a minimum re-treatment interval (RTI) of 6 days and a minimum PHI of 3 days.

Aventis response:

The current labels allow the application of 1 to 1.5 lb. ai/A on a 6- to 8-day interval. A maximum of 6-lb ai/A may be applied per season with a PHI of 3 days.

Page 4 Paragraph 2 Lines 1-2

EPA comment:

Use directions for olives on all labels should be amended to remove the statement allowing the use of a tank mix with summer oil.

Aventis response:

This change has been made on all Aventis CropScience product labels.

Page 4 Paragraph 3 Lines 1-3

EPA comment:

Based on acceptable residue data on prickly pear cactus from IR-4, the registrant should amend use directions on FIC and WP labels to specify a maximum of three applications per season at 2 lb ai/A/application at a minimum RTI of 7 days and a minimum PHI of 3 days.

Aventis response:

The current labels allow the application of 2 lb ai/A on a 7 to 10 day interval. A maximum of 6 lb ai/A may be applied per season with a PHI of 3 days.

GLN 860.1300: Nature of the Residue - Livestock

Page 5 Paragraph 4 Lines 2-6

EPA comment:

The registrant has stated its intention to support dermal uses on poultry and carbaryl uses in poultry houses and, according to REFS, these uses are on carbaryl labels. If the registrant intends to support these uses of carbaryl on poultry, tolerances, supported by adequate metabolism and magnitude of the residue data, will be required, at levels appropriate for these uses.

Aventis response:

Aventis CropScience will no longer support the use of carbaryl for direct application to poultry, as well as the poultry quarters treatment. We will submit a request for cancellation of these uses in accordance with section 6(f)(1) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).

GLN 860.1500: Crop Field Trials

Page 9 Paragraph 2 Lines 1-3

EPA comment:

Adequate data are available to reassess the tolerances for residues of carbaryl in/on sugar beet roots and tops provided that use directions on five currently approved labels are modified to allow a maximum of two applications per season at 1.5 lb ai/A/application and a PHI of 28 days

Aventis response:

The labels were amended to conform to these requirements.

Page 10 Paragraph 3 Lines 1-2

EPA comment:

Adequate data are available on olives provided that use directions for olives are amended to remove the statement allowing the use of summer oil as an adjuvant.

Aventis response:

The labels were amended to conform to this requirement.

Page:10 Paragraph 5 Lines 2-3

EPA comment:

Additional data are required depicting carbaryl residue in/on cotton gin byproducts.

Aventis response:

Aventis is not supporting the cotton use and has removed this crop from the labels.

Page:10 Paragraph 6 Lines 1-4

EPA comment:

The registrant does not intend to support carbaryl on avocados, barley, maple sap, oats, rye, and sweet sorghum; however, IR-4 has indicated (correspondence from K. Dorschner, IR-4 Project, 9/15/94) that they may fulfill the residue data requirements for some of these commodities. These data have not been submitted.

Aventis response:

IR-4 has not generated the residue data necessary to support these uses. Aventis CropScience will not support these uses.

Table A2. Food/Feed Use Patterns on EP Labels Subject to Reregistration for Carbaryl (Case 0080)

Page: 16

EPA comment:

Maximum Single Application Rate, ai: 3.0 lb/A & 4.0 lb/A (CA only).

Aventis response:

Maximum Single Application Rate, ai: 3.0 lb/A & 4.0 lb/A (CA only). An additional application at the dormant or delayed dormant timing may be made at a maximum rate of 5 lb/A.

Page: 21 Site: Beet, Sugar

EPA comment:

The maximum seasonal rate for sugar beets is 4.0-lb ai/A.

Aventis response:

The rate for the 80 WSP is 4.0-lb ai/A. however, the maximum seasonal rate for flowable formulations to sugar beets is 3.0 lb ai/A.

Page: 23 Site: Broccoli, Brussels sprouts, etc.

EPA comment:

The preharvest interval for broccoli, Brussel sprouts, cabbage, cauliflower, Chinese cabbage, collards, kale, kohlrabi, and mustard greens is 3 days.

Aventis response:

The preharvest interval for broccoli, Brussel sprouts, cabbage, cauliflower, and kohlrabi is 3 days. The preharvest interval for Chinese cabbage, collards, kale, and mustard greens is 14 days.

Page: 26 Site: Citrus fruits

EPA comment:

The maximum seasonal rate to Citrus Fruits in CA is 20.0 lbs/A

Aventis response:

The maximum seasonal rate to Citrus Fruits in CA is 16.0 lbs/A

Part IV - Occupational and Residential Exposure/Risk Assessment

Line-by-Line Review of the Supporting Document "Carbaryl: Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document (Jeffrey L. aDawson; June 28, 2001)"

1.0 Occupational and Residential Exposure/Risk Assessment

1.3 Summary of Hazard Concerns

Page: 12 Table 1:

EPA comment:

UF column for short-term dermal, inhalation & non-dietary ingestion reads "3000 for residential and 300 for occupational"

Aventis response:

This box should read, "3000 for residential and 300 for occupational,+ dermal absorption factor" for consistency purposes. However, for the reasons previously stated the extra 10X and 3X MOS factors should be removed due to the recently submitted toxicological studies.

EPA comment:

UF column for intermediate-term dermal, inhalation & non-dietary ingestion reads "1000 for residential and 100 for occupational" and the Type of Exposure column refers only to dermal exposure.

Aventis response:

The UF box should read, "1000 for residential and 100 for occupational,+ dermal absorption factor" for consistency purposes. The 1000X MOS factor should be reduced as the extra 10X MOS is no longer necessary. In addition, the Type of Exposure box should read "Intermediate-term dermal, inhalation, & non-dietary ingestion" for accuracy.

2.0 Occupational Exposures and Risk

2.1.2 Data and Assumptions for Handler Exposure Scenarios
Occupational Handler Exposure Studies

Page:34 Paragraph: 3 Note to Chemical Review Managers:

EPA comment:

" There are no data compensation issues associated with the use of …the propoxur trigger sprayer study has a signed PHED data waiver but just has not been included into PHED at this time.

Aventis response:

Although Bayer has submitted a data compensation waiver for the inclusion of the propoxur study in PHED, the data compensation waiver is applicable only to the data cited once in PHED. Specifically, the first paragraph of the data compensation waiver form states, '*The following pertains only to those data taken from company studies and incorporated into the generic exposure monitoring database'*. In addition, the 29 December 1986 memorandum from Douglas Campt, Director of OPP to pesticide registrants regarding the formation of PHED, specifically states on page 2, bullet point 1 *Those companies who submit data for inclusion in the data base will waive their compensation rights under FIFRA to the data when referenced generically as part of the data base. However, existing compensation rights will apply when a company's data is cited specifically.*

Aventis concludes that the specific referencing of the Bayer propoxur exposure study rather than a PHED generic study number does not eliminate the data compensation rights of Bayer. Aventis believes that the Health Effects Division should seek specific guidance from the Office of General Counsel regarding the data compensation status of the propoxur study for use in the carbaryl RED.

2.0 Occupational Exposures and Risk

2.1.2 Data and Assumptions for Handler Exposure Scenarios

Page: 32 Paragraph: First bullet Line 2:

EPA comment:

If additional information such as average or typical rates are available, these values are used as well in order to allow risk managers to make a more informed risk management decision. Average application rates were available from the SMART meeting and BEAD's QUA. These data indicate that in most cases, average application rates differ from maximum application rates on average by a factor of two. For example, when interpreting the results of the cancer assessment, the small differences generally seen in the available rates should be considered along with the overall magnitude of the cancer risk results.

Aventis response:

Aventis believes that the average or typical application rates provided in the document should be used in the determination of intermediate-term, chronic, and cancer risk assessments. The use of the label maximum application rates for each application becomes extremely unlikely for intermediate term grower exposure assessments of 10 applications, commercial intermediate-term assessments of 30 applications, and chronic or cancer risk assessments. Although the Agency may believe it is obligated to look at the maximum application rates for exposure durations longer than the short-term assessments, it should as it states provide

estimates of risk based on average application rates for the intermediate-term and longer risk assessments. Appendix C provides and utilizes only label maximum application rates for the estimation of intermediate-term and chronic MOEs in Tables 3, 4, 5, 6, 8, 9, 10, and 11. The risk assessment must provide MOEs based on average application rates to allow risk managers to make a more informed risk management decision.

2.0 Occupational Exposures and Risk

2.1.2 Data and Assumptions for Handler Exposure Scenarios

Page: 42 Table 9:

EPA comment:

LCO Turfgun exposure estimates obtained from ORETF study OMA002 are based on the wettable powder formulation data. The dermal exposure estimates are 0.99 mg/lb a.i., 0.72 mg/lb a.i., and 0.38 mg/lb a.i. for single layer no gloves, single layer gloves, and double layer gloves clothing scenarios, respectively. Inhalation exposure is 0.062 mg/lb a.i. The Table 9 footnote states *WP formulation used for turfgun assessment as the unit exposures for this scenario were slightly higher than for the other formulations (i.e., well within a factor of 2)*.

Aventis response:

Sevin is sold to the professional lawn care market as either an 80S in water soluble packaging or as the SL liquid formulation. Therefore, the use of the wettable powder formulation is not appropriate. Therefore, the dermal exposure for the single layer of clothing and glove scenario should be 0.66 mg/lb a.i. based on all formulations and the inhalation exposure should be 0.007 mg/lb a.i. based on the higher water-soluble packaging estimate compared to the flowable liquid inhalation exposure estimate of 0.002 mg/lb a.i.

2.3 Occupational Risk Characterization

2.3.1 Handler Characterization

Page: 103 Paragraph: 2 Line: 19

EPA comment:

Where available, average use rates were also used to provide for a more informed risk management decision

Aventis response:

While Aventis agrees that average use rates should be used for intermediate-term and longer repeated exposure risk assessments, the use of average application rates in the exposure assessments does not appear evident. The MOEs presented for intermediate-term and longer risk are based on label maximum application rates. The position of Aventis is that handler MOEs for intermediate-term and

longer risk assessments should be based on average application rates and not label maximum rates as presented in the assessment.

3.0 Residential and Other Non-Occupational Exposures and Risks

3.1.1 Handler Exposure Scenarios

Page: 116 Table 27:

EPA comment:

Table 27 states that *Hose-end sprayer data for mix your own (not the locking/no contact package) considered.*

Aventis response:

The dermal and inhalation exposure estimates of 2.61 mg/lb a.i. and 0.010 mg/lb a.i., respectively, for the ready-to-use (RTU) hose end sprayer need to be included in the handler exposure scenario estimations of homeowner exposure during application to lawns. The use of the product in this packaging results in exposure estimates that are different than the dial type sprayer (DTS). Because the RTU sprayer is a significant method of lawn application, the consideration of the potential exposure and risk for lawn applications with the RTU sprayer need to be presented and discussed in the risk assessment. The difference in exposure potential between the DTS and RTU hose-end sprayers may provide important information for risk management decisions that are currently lacking.

3.0 Residential and Other Non-Occupational Exposures and Risks

3.1.3 Residential Handler Exposure and Non-Cancer Risk Estimates

Page: 122 Table 28:

EPA comment:

Scenario 3, Fire Ant MOEs are based on the use of 100 gallons or 0.75 lb a.i./event for the garden vegetable hose-end spray scenario and 5 gallons or 0.0375 lb a.i./event for garden low pressure handwand applications.

Aventis response:

Aventis does not understand why there is a 20-fold difference in the amount of active ingredient handled between the hose-end sprayer and hand wand application of carbaryl to control fire ants at the same site, gardens. Aventis believes that the use of 0.0375 lb a.i./event is reasonable for a vegetable garden and that the use of 100 gallons of spray or 0.75 lb a.i./A is more representative of a lawn spot application to control fire ants. Scenario 3, Fire ant vegetable garden use should be reduced to 0.075 lb a.i./event, which is similar to the other scenario 3 vegetable garden uses and consistent with the fire ant control in vegetable gardens using the low pressure hand wand equipment. Any estimation of fire ant

control on the lawn should be based on exposure data from the ORETF hose-end sprayer exposure study (OMA004) and not from the carbaryl vegetable garden exposure study (MRID 44459801).

3.0 Residential and Other Non-Occupational Exposures and Risks

3.1.4 Residential Handler Exposure and Risk Estimates for Cancer

Page: 128 Table 29:

EPA comment:

Presentation of cancer risks to three significant figures.

Aventis response:

Aventis does not believe that the expression of cancer risks to three significant figures accurately portrays the lack of precision in the risk assessment. Cancer risks should be presented as either one or two significant figures, consistent with HED policy. The use of three significant figures is leading to the portrayal of cancer risks such as 1.08×10^{-6} for fire ants or 1.24×10^{-6} for vegetable garden dusts as being in excess of the 1×10^{-6} guideline. Both of these risks are more correctly presented as 1×10^{-6} to present the lack of precision in the cancer risk assessment.

Appendix F: Carbaryl Residential Handler Exposure Data

Table 2. Input Parameters for Carbaryl Homeowner Handler Exposure and Risk Calculations

EPA comment:

Inhalation unit exposures are estimated based on a breathing volume of 29 l/min.

Aventis response:

The recommended breathing volume for adult short-term exposure is 1.0 m^3/hr or 17 l/min for light activities (U.S. EPA Exposure Factors Handbook, Volume 1 General Factors, EPA/600/P-95/002Fa). In discussions between the ORETF and the regulatory advisory board to ORETF, it was agreed that application of home pesticide products constituted light activities and that the 17 l/min breathing rate will be used. The 29 l/min rate used by HED is the PHED default and represents agricultural work practices that are more strenuous than home pesticide application. Therefore, all residential inhalation exposure estimates should be based on 17 l/min breathing volume or 59% of the inhalation exposure estimates presented in the HED assessment.

Part IV - Occupational and Residential Exposure/Risk Assessment

SUPPORTING DISCUSSION

Occupational and Residential Exposure Assessment

The assessment of occupational and residential exposure and risk prepared by Mr. Jeff Dawson was a comprehensive assessment of excellent quality. This is reflected by the relatively minimal number of factual error comments provided by Aventis CropScience. Based on the quality of the initial assessment, the major effort regarding the assessment of occupational and residential exposure to carbaryl will involve refinement of the risk assessment.

Aventis CropScience has conducted, or is in the process of conducting, studies relevant to the refinement of the occupational and residential risk assessment. These studies are as follows:

- 4-Week Repeated-Dose Dermal Toxicity Study with Sevin XLR Plus in Rats. The study is completed and a draft report is currently in review by Aventis. The results of this study are intended to replace the current dermal exposure toxicity endpoints based on oral toxicity used for short-term and intermediate-term occupational and residential handler exposure when handling liquid formulations of carbaryl.
  Expected completion date: September 2001
- 4-Week Repeated-Dose Dermal Toxicity Study with Sevin 80S in Rats. The study is completed and a draft report is currently in review by Aventis. The results of this study are intended to replace the current dermal exposure toxicity endpoints based on oral toxicity used for short-term and intermediate-term occupational and residential handler exposure when handling solid formulations of carbaryl.
  Expected completion date: September 2001
- 4-Week Repeated-Dose Dermal Toxicity Study with Carbaryl Technical in Rats. The study is completed and a draft report is currently in review by Aventis. The results of this study are intended to replace the current dermal exposure toxicity endpoints based on oral toxicity used for short-term and intermediate-term occupational and residential postapplication dermal exposure.
  Expected completion date: September 2001
- Measurement of Pesticide Exposure of Suburban Residents Associated with the Residential Use of Carbaryl. This is an ongoing biological monitoring study of 10 families in California and 10 families in Missouri. The study will monitor the absorbed dose of carbaryl resulting from a lawn broadcast application and subsequent vegetable garden application of carbaryl by an adult family member. Postapplication absorbed dose of all adults and children aged four to seventeen will be followed over a three-day period. The participants' postapplication activities will be recorded but not controlled to establish a range of absorbed

doses. The data will be used along with the residential exposure assessment to improve understanding of residential exposure to carbaryl.
Expected completion date: March 2002

- University of California - Riverside biological monitoring of citrus orchard application and postapplication apple thinning and cherry harvesting job functions is completed in the field. The results from these studies will be used to refine the PHED and ARTF-based exposure estimates. These are high exposure potential work functions and the biological monitoring data are intended to refine the assessments of these work functions.
Expected completion date: March 2002

APPENDIX I

Business Confidential

Surface Water Monitoring for Residues of Carbaryl in High Use Areas of the United States (Stone Environmental, Inc. Report #99-1005-F) (hard copy provided)

CARBARYL

PC Code No. 056801; Case 0080

Review of the Draft Environmental Fate and Ecological Risk Assessment for the Reregistration of Carbaryl

August 6, 2001

Aventis CropScience
P.O. Box 12014, 2 T.W. Alexander Drive
Research Triangle Park, NC 27709

CARBARYL

PC Code No. 056801; Case 0080

Review of the Draft Environmental Fate and Ecological Risk Assessment for the Reregistration of Carbaryl

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Confidential Business Attachments

The last page of this report is number 70 \# "0" 70.

General Comments

The EFED draft chapter of the carbaryl RED is very thorough using a wealth of references. The use of published literature over submitted data is significant. The quality of the published literature is at times at least questionable and other times does not fulfill the requirements set by EPA for studies submitted by the registrant (e.g. thorough description of test conditions, clear identification of the test material, analytical verification, GLP etc.). Data of such poor quality should not be used as key information in the risk assessment. For the 30-day response not all literature references could be verified or the quality ascertained.

There is a high level of redundancy in the document making it difficult to read. Reducing repetitions to a minimum would facilitate the reading.

We believe it is inappropriate to include DERs in the RED Chapters. A summary of study findings is already presented in the document. DERs should be made available to the public through the regular procedure under the Freedom of Information Act after they have been reviewed and cleared for confidential business information.

The use of carbaryl on barley, oats, rye, cotton, and livestock are cancelled . It should be noted that Aventis CropScience labels for the technical materials and the end-use products containing carbaryl were amended to delete these uses. The Agency has already approved the labeling changes (please refer to HED response document, Section III for details).

Aventis CropScience will no longer support the use of carbaryl on poultry (direct application and poultry quarters treatment). We will shortly submit a request for cancellation of these uses in accordance with section 6(f)(1) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) (please refer to HED response document, Section III for details).

Aventis CropScience is in the process of conducting, or has scheduled, studies relevant to the refinement of the environmental risk assessments for carbaryl and the major degradate 1-naphthol. These studies are as follows:

- Rate and Route of Aerobic Degradation in Soils. These studies have been initiated with parent carbaryl applied to four diverse U.S. soils. The data are intended to provide additional half-life determinations for parent carbaryl and the major degradate 1-naphthol.
  Expected completion date: March 2002
- Aerobic Aquatic Metabolism in Two Water/Sediment Systems. These studies have been initiated with parent carbaryl applied to two distinct U.S. water/sediment systems. The data are intended to provide additional half-life determinations for parent carbaryl and the major degradate 1-naphthol. In addition, further identification of additional degradation products is anticipated.
  Expected completion date: March 2002
- Adsorption and Desorption of 1-Napthol to five soils. This study has been scheduled to evaluate the adsorption and desorption of the major carbaryl degradate to five soils/sediment. The data are intended to provide information necessary to evaluate the

environmental risks from 1-naphthol in standard models.
Expected completion date: March 2002

For the reregistration process in the EU, Aventis CropScience is in the process of conducting, or has scheduled, studies relevant to the refinement of the ecotoxicological risk assessments for carbaryl and the major degradate 1-naphthol. These studies are as follows:

- Studies with Carbaryl:

  Acute oral LD50 in mallard ducks
  Dynamic acute LC50 in bluegill sunfish
  Acute toxicity in *Daphnia*
  Acute toxicity in *Chironomus riparius*
  Toxicity in *Selenastrum capricornutum*
  Acute oral and contact toxicity in honeybees
  14-d toxicity in earthworms
  Effects on soil microorganisms (nitrification/carbon cycle)
  Effect on sewage treatment

- Studies with 1-naphthol

  Early life-stage study in fathead minnow
  Acute toxicity in *Daphnia*
  Acute toxicity in *Daphnia* in presence of sediment
  Chronic toxicity in *Daphnia*
  14-d toxicity in earthworms

- Formulated Product

  Vegetative Vigor
  Toxicity in *Selenastrum capricornutum*
  Acute oral and contact toxicity in honeybees
  Effect on non-target arthropods
  14-d toxicity in earthworms
  Effects on soil microorganisms (nitrification/carbon cycle)

Ecotoxicological Risk Assessments

Aventis has pointed out several errors in the PRZM input parameters (see comments made to Tables 5 and 6 of the draft RED), overly conservative estimates of foliar dissipation half-lives and changes in ecotoxicology study endpoints. This indicates that a re-calculation of the EECs and risk quotients are warranted in a number of instances.

Endocrine Disruption

Reports in the open literature on the reproductive effects of carbaryl in wild mammals are at best ambivalent. The recently submitted 2-generation study in rats demonstrates the absence of

reproductive effects. As EPA pointed out, findings reported in the literature were made at concentrations well above the highest peak concentration modeled. Therefore these findings are irrelevant for a risk assessment and at the current stage of discussion about endocrine disruption. If the concern about the endocrine potential of carbaryl persists, the issue should be revisited once the Agency's endocrine disrupter screening and testing program as well as a policy on how to incorporate positive findings into an ecological risk assessment have been fully developed.

Mobility

The classification of carbaryl as mobile to very mobile is inconsistent with measured K_{oc} values of 177 to 249 (MRID 43259301). According to the widely used classification scheme of McCall, *et al.* (1980) wherein K_{oc} values between 150 and 500 denote medium mobility in soil, carbaryl would be classified as having medium mobility in most soils. This classification of medium mobility is further supported by the acceptable column leaching study (MRID 43320701) in which aged carbaryl residues were only slightly mobile in a number of soils. The mobility of carbaryl would be expected to be higher in sandy soils or in soils of low organic matter.

1-Napthol Fate and Transport

The Agency is requiring additional information on the persistence and mobility of 1-naphthol, a major environmental degradate of carbaryl. However, a half-life for 1-naphthol of less than 1 day can be calculated from the carbaryl aerobic soil metabolism study (MRID 42785101). The data from this study demonstrate that under aerobic soil conditions the formation and decline of 1-naphthol, starting from parent carbaryl, is complete in less than 14 days. This half-life can be used for preliminary environmental fate modeling to estimate EECs for 1-naphthol.

The EPA suggested that 1-naphthol is not strongly sorbed to soil. Additional information available in the literature demonstrates that the sorption of 1-naphthol to soil is stronger than that seen for carbaryl itself. Hassett *et al.* (1981) has demonstrated that the sorption of 1-naphthol was the result of sorption to organic carbon resulting in K_{oc} values between 431 and 15,618. These data indicate that 1-naphthol is less mobile and less susceptible to leaching than carbaryl itself, and they demonstrate that at least a portion of the 1-naphthol residue is tightly sorbed to soil constituents. (A copy of this article is being submitted with the response to the draft RED.) To meet the requirement for information on the adsorption and desorption of 1-naphthol by the Agency, the registrant is conducting an adsorption/desorption study to meet the 163-1 guideline. Study results should be available for submission to the Agency in the first quarter of the calendar year 2002.

Surface Water/Drinking Water

Aventis disagrees with EPA that the modeling simulations provide a conservative, though not unreasonable, estimate on possible concentrations in drinking water. Drinking water concentrations derived from PRZM/EXAMS greatly overestimate the potential exposure to carbaryl in drinking water, generally by several orders of magnitude. Results from the drinking

water monitoring program conducted by the registrant provides a 'real world' assessment of the potential for human exposure to carbaryl in drinking water derived from surface water.

Ground Water

EPA summarized information on the detection of carbaryl in groundwater from the EPA Pesticides in Groundwater Database, the EPA STORET database and the NAWQA database. Each of the databases shows a pattern of very low levels of carbaryl detection in few groundwater resources. These analyses confirm several statements made by the Agency that carbaryl have limited potential to impact groundwater resources. However, on page 2 of the Memorandum issued June 28, 2001, in conjunction with the EFED RED chapter for carbaryl, EPA is requiring additional information on "Surface and groundwater monitoring in urban and suburban use areas (non-guideline)." Based on the characteristics of carbaryl and the available data demonstrating limited impact of carbaryl on ground water resources, additional studies to evaluate the potential for carbaryl to contaminate groundwater are unnecessary and unwarranted.

Line-by-Line Review of the Carbaryl EFED RED Chapter

Transmittal Document

Data Gaps

Environmental Fate and Transport

Page: 2 Paragraph: 1 Line: 1

EPA comment:

Fate information on the degradation product 1-naphthol is required.

1. Mobility – adsorption and desorption studies for the 1-naphthol degradate (163-1)
2. Persistence – aerobic soil metabolism study on 1-naphthol

Aventis' response:

Literature data (Hassett *et al*. 1981) on the adsorption of 1-naphthol are provided in this response. Aventis is in the process of conducting an additional adsorption/desorption study on 1-naphthol and intends to submit study data to EPA by March 2002.

The degradation of 1-naphthol under aerobic soil conditions has been widely reported in the literature. Several citations are included in the EPA draft RED. The half-life of 1-naphthol estimated from the acceptable aerobic soil persistence study on carbaryl (MRID 42785101) is less than 1 day. Aventis is conducting additional laboratory aerobic soil degradation studies on carbaryl that will be used to provide additional determinations of the half-life for the degradate 1-naphthol and satisfy the Agency's requirement for data on the persistence of 1-naphthol. Aventis intends to submit these study data to EPA by March 2002.

Water Resources

Page: 2 Paragraph: 3 and 4

EPA comment:

"*EFED believes that adequate data are available to support the conclusions reached for carbaryl's impact on surface water and groundwater quality with the exceptions noted below. Additional information is needed to characterize the impact of the degradate 1-naphthol [in] groundwater and surface water. …Surface and groundwater monitoring in urban and suburban use areas (non-guideline)"* are required.

Aventis' response:

The surface water-monitoring program conducted by Aventis includes monitoring in urban and suburban use areas. Aventis believes that the need for information on the degradate 1-naphthol will be satisfied by the aerobic soil and adsorption/desorption data that will be submitted to the Agency. These data can be used to evaluate the availability of 1-naphthol using established EPA modeling guidelines. The Agency's proposed requirement for groundwater monitoring is unnecessary and is addressed in Aventis' response to Agency comments in the draft RED.

Ecological Effects Data requirement

Page: 2

EPA comment:

The ecological toxicity database is complete except for:

6. Aquatic Plant Growth Guideline 122-2

Aventis' response:

The data requirement should be deleted. Aquatic plant growth studies were submitted to the Agency in 1992. An October 04, 2000 OPP Guideline Status Report (Chemical Review Management System) lists the guideline 122-2 status as "Acceptable/Satisfied". The studies are:

MRID No.	Title	Acceptability Code
42372101	Lintott, D. (1992) Carbaryl Technical: Acute Toxicity To The Freshwater Blue- Green Alga, *Anabaena flos-aquae*, Under Static Test Conditions: Lab Project Number: J9112004E. Unpublished Study Prepared By Toxikon Environmental Sciences. 53 P. *June 25, 1992*	Upgradable
42372102	Lintott, D. (1992) Carbaryl Technical: Acute Toxicity To Duckweed, *Lemna gibba* G3, Under Static Test Conditions: Lab Project Number: J9112004G. Unpublished Study Prepared By Toxikon Environmental Sciences. 53 P. *January 1, 1992*	Upgradable
42372802	Lintott, D. (1992) Carbaryl Technical: Acute Toxicity To The Freshwater Green Alga, *Selenastrum capricornutum* Under Static Conditions: Lab Project Number: J9112004C. Unpublished Study Prepared By Toxikon Environmental Sciences. 53 P. *June 9, 1992*	Acceptable
42431601	Lintott, D. (1992) Carbaryl Technical: Acute Toxicity To The Freshwater Diatom, *Navicula pelliculosa*, Under Static Test Conditions: Lab Project Number: J9112004F. Unpublished Study Prepared By Toxikon Environmental Sciences. 52 P. *August 10, 1992*	Acceptable
42431602	Lintott, D. (1992) Carbaryl Technical: Acute Toxicity To The Saltwater Diatom, *Skeletonema costatum*, Under Static Test Conditions: Lab Project Number: J9112004D. Unpublished Study Prepared By Toxikon Environmental Sciences. 49 P. *August 10, 1992*	Supplemental

Page: 2

EPA comment:

The ecological toxicity database is complete except for:

7. Submission of a FETOX amphibian toxicity study is required.

Aventis' response:

The data requirement should be deleted. From the published results it is evident that carbaryl is practically non-toxic to the bullfrog. Effects in plain leopard frogs are reported at levels well above environmental concentrations. These results were obtained testing U.S. native species. In the proposed FETOX assay, a non-native species *Xenopus laevis* is used. This African species is unique in its behavior. Neither the species nor the test methods are suitable for ecotoxicological purposes. As the risk to amphibians can be evaluated from the studies cited, and as the effects are only at levels well above the EEC, this study should not be required.

Label Information

Page: 3

EPA comment:

For terrestrial and residential uses:

1. "Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Do not contaminate water when disposing of equipment washwater or rinsate."

Aventis' response:

Similar language is already present on Aventis' SEVIN® labels.

Page: 3

EPA comment:

For terrestrial and residential uses:

3. "This product may contaminate water through drift of spray in wind. This product has a high potential for runoff for several days after application after application (sic). Poorly draining soils and soils with shallow water tables are more prone to produce runoff that contains this product.

   Household labels – Avoid applying this product to ditches, swales, and drainage ways. Runoff of this product will be reduced by avoiding applications when rainfall is forecasted to occur within 48 hours.

   Agricultural Label – A level, well maintained vegetative buffer strip between areas to which this product is applied and surface water features such as ponds, streams, and springs will reduce the potential for contamination of water from rainfall-runoff. Runoff of this product will be reduced by

avoiding applications when rainfall is forecasted to occur within 48 hours."

Aventis' response:

Aventis would like to further discuss appropriate label language with the Agency. However, it should be noted that light to moderate rainfall (or irrigation) after application will also help move carbaryl residues deeper into the soil, thus making them less susceptible to runoff. The language in the last sentence should be changed to read, "…when *heavy* rainfall is….".

Page: 3

EPA comment:

For terrestrial and residential uses:

4. This pesticide is toxic to fish and aquatic invertebrates.

Aventis' response:

Aventis' SEVIN labels currently state "This product is extremely toxic to aquatic and estuarine invertebrates."

Page: 3

EPA comment:

For terrestrial and residential uses:

5. This product is highly toxic to bees exposed to direct treatment or residues on blooming crops or weeds. Do not apply this product or allow it to drift to blooming crops or weeds if bees are visiting the treatment area.

Aventis' response:

Aventis' SEVIN labels currently contain similar language.

Draft RED Document

1.0 Summary and Environmental Risk Conclusions

Risk to Terrestrial Organisms

Page: 1 Paragraph: 4 Line: 2

EPA comment:

As discussed in pp. 44 - 45 and in Appendix D.

Aventis' response:

The mammalian risk quotients are discussed on pages 48 to 50 and in Appendix C, not as described in this text.

Fate and Water Assessment

Page: 3 Paragraph: 5 Line: 3

EPA comment:

…in the U.S.G.S NAQWA program. NAQWA…

Aventis' response:

The abbreviation for the U.S.G.S. program is NA**WQ**A

Page: 5 Paragraph: 1 Line: 7

EPA comment:

…estimate of possible concentrations drinking water.

Aventis' response:

missing word – …concentrations "in" drinking…

Page: 5 Paragraph: 4 Line: 4

EPA comment:

…hydrolyzes in neutral (half-life = 12 days) and alkaline environments (pH 9 half-life = 3.2).

Aventis' response:

Missing units of after second half-life. The units are hours, so "= 3.2 hours)".

Page: 5 Paragraph: 4 Line: 5

EPA comment:

…photolysis in water with a half-life of 21 days

Aventis' response:

this is for photolysis in sterile water, not microbially-active water, so the phrase would be more precise as "…photolysis in sterile water…".

Page: 5 Paragraph: 4 Line: last

EPA comment:

(K_f =1.7 to 3.2).

Aventis' response:

The upper value K_f for carbaryl should be listed as 3.5 as referenced by EPA elsewhere (e.g. Table 3, page 20) in the document.

2.0 Introduction

Page: 6 Paragraph: 2 Line: 1-3

EPA comment:

Carbaryl (1-naphthyl N-methylcarbamate) is a broad-spectrum carbamate insecticide and acaricide registered for control of over 300 species of insects and mites on over 100 crop and noncrop use sites, including homeowner uses; pet, poultry, and livestock uses;…

Aventis' response:

Carbaryl is no longer registered for use on livestock. Aventis CropScience will not support the reregistration of the use on poultry (direct application and poultry quarters treatment). We will shortly submit a request for cancellation of this use in accordance with section 6(f)(1) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).

Page: 6 Paragraph: 3 Line: 2-3

EPA comment:

Approximately 2.5 million pounds of carbaryl are applied annually in the U.S. A map showing the widespread use of carbaryl in agriculture is shown in figure 1.

Aventis' response:

Summation of the data in Figure 1 gives a total of approximately 3.3 million pounds of carbaryl. Both the 2.5 and 3.3 million-pound figures are inconsistent with the value of 4 million pounds cited on page 35. The 2.5 million pounds is an average of usage over 1987 to 1996 developed in a memo by Frank Hernandez, July 21, 1998. The value of 2.5 million pounds in the text should be qualified with the additional information on the fact that it is an average for usage over 1987 to 1996 and is not a value for a single year.

Page: 7 Paragraph: 1 Line: 3-4

EPA comment:

Carbaryl is also used extensively for residential and other non-agricultural uses, being the second most commonly insecticide (sic) used in the home.

Aventis' response:

Carbaryl is not registered for use inside homes. It is registered for use outdoors in the lawn and garden around homes. In addition, an evaluation of the Vista (Triad) data for the last seasonal year from October 1999 to September 2000 shows retail sales for carbaryl at 18.7 million dollars. Carbaryl is listed as number 7 based on retail sales behind other active ingredients such as chlorpyrifos, diazinon, imidacloprid, hydramethylnon and tralomethrin. Therefore this sentence would be more appropriately worded as: "Carbaryl is also used for residential and other non-agricultural uses, being the seventh most commonly used insecticide around the home."

Page: 7 Figure 1

EPA comment:

Figure 2

Aventis' response:

This is labeled as Figure 2 when it is Figure 1

3.0 Integrated Risk Characterization

Introduction

Page: 8 Paragraph: 1 Line: last

EPA comment:

Carbaryl is mobile to very mobile in the environment (K_f =1.7 to 3.2).

Aventis' response:

The upper value K_f for carbaryl should be listed as 3.**5** as referenced by EPA elsewhere (e.g. Table 3, page 20) in the document. The classification of carbaryl as mobile to very mobile is inconsistent with measured K_{oc} values of 177 to 249. According to the widely used classification scheme of McCall *et al.* carbaryl would be classified as having medium mobility in soil. This classification of medium mobility is further supported by the acceptable column leaching study (MRID 43320701) in which carbaryl residues were only slightly mobile in a number of soils.

Aquatic Organisms

Page: 10, Paragraph: 1, Line: 13

EPA comment:

Submission of a FETOX amphibian toxicity study is encouraged.

Aventis' response:

The data requirement should be deleted. From the published results it is evident that carbaryl is practically non-toxic to the bullfrog. Effects in plain leopard frogs are reported at levels well above environmental concentrations. These results were obtained testing U.S. native species. In the proposed FETOX assay a non-native species *Xenopus laevis* is used. This African species is unique in its behavior. Neither the species nor the test methods are suitable for ecotoxicological purposes. As the risk to amphibians can be evaluated from the studies cited, and as the effects are only at levels well above the EEC, this study should not be required.

Page: 10, Paragraph: 3, Line: 6/7

EPA comment:

…resulting in a temporary impairment of burying behavior and increasing exposure to predators.

Aventis' response:

A reference for this statement should be added.

Page: 11, Paragraph: 2, Line: 7

EPA comment:

In a mesocosms study, at carbaryl…

Aventis' response:

Typographical error. Change to "In a mesocosm study, at carbaryl…"

Terrestrial Organisms

Page: 12 Paragraph: 2

EPA comment:

(use of rock dove LD50)

Aventis' response:

The reference cited for this value in Table 1 of Appendix D is currently not available to Aventis. Table 1 of Appendix D gives a range of 1000 – 3000 mg/kg for the LD50. It should be assured that 1000 is indeed the correct value.

Page: 12 Paragraph: 3 Line: 3 - 6

EPA comment:

On a chronic basis, the NOAEC is 300 ppm for the mallard duck, based on adverse reproduction effects, including reduced egg production, decreased fertility, increase incidence of cracked eggs, increased embryonic mortality, and reduced hatching success.

Aventis' response:

The sentence should be changed. The embryonic mortality and the hatching success were not different from the control.

Page: 13 Paragraph: 1 Line: 1

EPA comment:

…(rat LD_{50} = 307 mg/kg)

Aventis' response:

Typographical error, the LD_{50} is 301 mg/kg.

Page: 13 Paragraph: 1 Line: 2 – 4

EPA comment:

…based on decreased fetal body weights and increased incomplete ossification of multiple bones in the laboratory rat (LOAEC = 600 ppm, NOAEC = 80 ppm), has the potential for mammalian chronic effects.

Aventis' response:

A new chronic reproduction study in rats has been submitted by Aventis. This study is more relevant for an ecological risk assessment than the developmental study cited. The new study resulted in a NOAEC of 75 ppm.

Page: 13 Paragraph: 3 Line: 1

EPA comment:

Information available in the open literature suggests potential reproduction effects of carbaryl on mammals.

Aventis' response:

The sentence should be changed or deleted. The literature cited in the paragraph show ambivalent results. While some references seem to support that sentence, other references do not substantiate such a claim. The potential for reproductive effects in mammals is evaluated in the recently submitted 2-generation study in rats. No reproductive effects were seen in that guideline study. The NOAEC of 75 ppm was based on pup mortality.

Page: 13 Paragraph: 4 Line: 5

EPA comment:

According to surveys conducted by the American Beekeeping Federation and the Washington State Department of Agriculture, carbaryl is one of the pesticides most frequently mentioned as being associated with bee kills.

Aventis' response:

A reference should be provided for this statement.

Page:14 Paragraph: 4 Line: 1-4

EPA comment:

The uses of carbaryl on crops (corn, cotton, soybeans, sorghum, wheat, barley, oats, and rye), forests and pasture/rangeland were addressed by the US Fish and Wildlife Service (USFWS) in the reinitiation of consultation in September 1989. The Service found jeopardy to a total of 86 species – 6 amphibians, 47 freshwater fish, 27 freshwater mussels, and 5 aquatic crustaceans.

Aventis' response:

The use of carbaryl on barley, oats, rye, and cotton has been cancelled. It should be noted that all Aventis CropScience labels for the technical materials and the end-use products containing carbaryl were amended to delete these uses. The Agency has already approved the labeling changes. Findings from the assessment made by the USFWS should be reevaluated considering the cancellation of the use on barley, oats, rye, and cotton.

Page:14 Paragraph: 5 Line: 7

EPA comment:

The RPAs and RPMs in the 1989 B.O. may need to be reassessed…

Aventis' response:

The acronyms used should be explained.

Endocrine Disruption Concerns

Page:15 Paragraph: 3

EPA comment:

(Report on potential endocrine effects)

Aventis' response:

The paragraph should be deleted. As EPA pointed out, the findings reported in the literature were made at concentrations well above the highest peak concentration modeled. Therefore these findings are irrelevant for a risk assessment and at the current stage of discussion about endocrine disruption. If the concern about the endocrine potential of carbaryl persists, the issue should be revisited once the Agency's endocrine disrupter screening and testing program, as well as a policy on how to incorporate positive findings into an ecological risk assessment have been fully developed.

Page:15 Paragraph: 4

EPA comment:

Furthermore, a number of field and laboratory studies report reproduction effects with mammals, suggesting that the possibility of endocrine disruption effects on wild mammals should be further examined.

Aventis' response:

The statement should be deleted or modified. As pointed out above, reports on reproductive effects of carbaryl in the open literature are at least ambivalent. The recently submitted 2-generation study in rats demonstrated the absence of reproductive effects. If the general statement about the potential for endocrine disruption of carbaryl is maintained, references (or a cross-reference within the document) for the above claim should be provided.

Uncertainties

Page: 15 Paragraph: Last Line: 4

EPA comment:

In the absence of a valid two-generation rat reproduction study, mammalian chronic RQs were based on a rat prenatal development study NOAEC (MRID# 44732901).

Aventis' response:

A new two-generation study in rats was recently submitted.

4.0 Environmental Fate Assessment

Exposure Characterization

Page: 16 Paragraph: 3 Line: 8

EPA comment:

Environment (K_f =1.7 to 3.2).

Aventis' response:

The upper value K_f for carbaryl should be listed as 3.5 as referenced by EPA elsewhere in the document (e.g. Table 3, page 20).

Page: 16 Paragraph: 3 Line: last sentence

EPA comment:

Detailed discussion and reviews (DERs) of the studies that are included in this assessment are attached in Appendix A.

Aventis' response:

It is inappropriate to include the DERs in the RED.A summary of study findings is already included in the EFED Chapter. DERs should be made available to the public through the regular procedure under the Freedom of Information Act after they have been reviewed and cleared for confidential business information.

Page: 16 Paragraph: 4 Line: 4

EPA comment:

lower levels (generally less than 0.01 μ/L).

Aventis' response:

value missing units - (generally less than 0.01 μ**g**/L).

Page: 16 Paragraph: 5 Line: 4

EPA comment:

…monitoring data is of limited utility in developing EECs for ecological and human health risk assessment.

Aventis' response:

The drinking water monitoring program conducted by the registrant provides a real world assessment of the potential for human exposure to carbaryl in drinking water derived from surface water. Drinking water concentrations derived from PRZM/EXAMS greatly overestimate the potential exposure to carbaryl in drinking water, generally by several orders of magnitude.

Page: 17 Paragraph: 1 Line: 2-3

EPA comment:

The maximum rate was taken from the carbaryl labels.

Aventis' response:

It would be of benefit for the Agency to be explicit and list the carbaryl labels that were used to develop the maximum application rates for the model scenarios. The reference cited in the EFED Chapter regarding the use of carbaryl on crops indicate that current labels were not used for the Agency's assessment. Many of these crops have been deleted from Aventis' labels for a few years Application rates, number of applications per season, and PHI's also have changed for several crops on the labels.

Page: 17 Paragraph: 2 Line: 2

EPA comment:

For the Index Reservoir scenario using maximum label rates, acute EEC values ranged from about 10 µg/L from sugar beets to about 500 µg/L from citrus (Table 6).

Aventis' response:

Table 6 on page 33 shows a concentration of 19 µg/L for sugar beets treated with the maximum label rate of 2 x 1.5 lb ai, not 10 as stated in this sentence. A low EEC value of 9 µg/L for sugar beets results from the "maximum reported" application scenario of 1 x 1.2 lb ai/A.

Page: 17 Paragraph: 2 Line: 3

EPA comment:

Chronic EECs ranged from about 1 to 28 µg/L.

Aventis' response:

Table 6 on page 33 shows that this is correct when considering all of the model scenarios. However, either the same maximum label rate reference should be used as in the preceding sentence (in which case the minimum chronic EEC would be 2), or the basis for the preceding sentence should be changed from the maximum label rate to include all application scenarios to keep the comparisons consistent.

Page: 17 Paragraph: 2 Line: 8

EPA comment:

The results of the modeling provide an (sic) conservative, though not unreasonable, estimate on (sic) possible concentrations [in] drinking water.

Aventis' response:

It should be clear that Aventis' surface water monitoring program provides a more reasonable estimate of the potential drinking water exposure to carbaryl than the modeling numbers, which overestimate exposure by several orders of magnitude.

Page: 17 Paragraph: 2 Line: last

EPA comment:

…and model input and output files are attached in appendix B.

Aventis' response:

The PRZM input files for only the Index Reservoir drinking water modeling were provided as an electronic copy. The PRZM input files for the standard pond scenarios were not provided in the draft RED so Aventis could not assess the data. None of the output files were provided.

Page: 18 Figure 2

EPA comment:

Figure 1. Generalized carbaryl degradation pathway

Aventis' response:

This should be labeled Figure 2, not Figure 1.

Page: 19 Table 3

EPA comment:

Hydrolysis half-life at pH 9 stated to be 5 hours.

Aventis' response:

The study results, and the summary of the study presented on page 20, show the correct half-life at pH 9 to be 3.2 hours.

Page: 19 Table 3

EPA comment:

Aerobic Aquatic half-life - 4.9.

Aventis' response:

The Aerobic Aquatic half-life is 4.9 days

Page: 19 Table 3

EPA comment:

Soil metabolism $T_{1/2,}$ anaerobic, assumed stable

Aventis' response:

If this guideline is satisfied by the data submitted for guideline 162-3, it is not clear why the compound is assumed to be stable rather than having a half-life in line with the 72 days that resulted from the anaerobic aquatic study. Although this parameter plays a fairly insignificant role in estimating the amount of carbaryl available for runoff in the models, it could play a significant role if one were to use this value in estimating leaching potential in subsurface horizons.

Page: 20 Table 3

EPA comment:

Batch Equilibrium

1/n values ranged from 0.86-1.02

Aventis' response:

These values are for the desorption isotherms only. For the adsorption isotherms that were used to calculate the adsorption K_f and K_{oc} values listed in the table, the correct range of 1/n values are 0.78 to 0.84 as stated on page 22.

Page: 20 Table 3

EPA comment:

Foliar Dissipation

30 days Willis and McDowell, 1987

Aventis' response:

The foliar dissipation half-life listed by EFED is incorrect. Table IV of the Willis and McDowell review lists 10 foliar half-lives for various formulations of carbaryl applied to different crops. Five of these half-lives are for a study designed to evaluate a new analytical procedure for measuring carbaryl residues on plants. This study was conducted on plants grown in a greenhouse, with some of them receiving an unknown amount of simulated rainfall. These studies on greenhouse-grown plants should not be used to evaluate foliar persistence in the field. The foliar persistence of pesticides can be considerably different for residues on and in plants grown in greenhouses versus the field. Eliminating the half-lives for the greenhouse-grown plants results in the following half-lives for carbaryl on field plants: Cotton, 1.2, 1.3, 1.5 days; strawberry, 4.1 days; tomato 1.4 days. Therefore, the longest half-life of 4.1 days should be listed in this table.

Aventis intends to conduct a more thorough review of the data on the foliar dissipation of carbaryl and prepare a more detailed response during the 60-day public comment period.

Persistence

Microbially-Mediated Processes

Page: 21 Paragraph: 3 Line: 3

EPA comment:

with an initial concentration of 11.2 mg/L, degraded with a half-life of 4.0 days in sandy

Aventis' response:

The units for ppm soil concentration should be given as mg/kg.

Page: 21 Paragraph: 3 Line: 4-5

EPA comment:

The major degradate was 1-naphthol which further degraded rapidly to non-detectable levels within 14 days.

Aventis' response:

The data from this study demonstrate that under aerobic soil conditions the formation and decline of 1-naphthol, starting from parent carbaryl is complete in less than 14 days. The study data show an average maximum 1-naphthol level of 34.5% of applied carbaryl by day 1, declining to 2.8% by day 2, 0% by day 4, 0.2% by day 7 and 0% at day 14. These data suggest a preliminary half-life of less than 1 day for the major degradate 1-naphthol.

Page: 21 Paragraph: 3 Line: 8-9

EPA comment:

In anaerobic aquatic soil carbaryl with an about 10 mg/L degraded with a half-life of 72.2 days.

Aventis' response:

Several words appear to be missing from this sentence. One suggestion: "Carbaryl degraded with a half-life of 72.2 days in anaerobic aquatic sediment with an initial carbaryl concentration of about 10 mg/L."

Page: 22 Paragraph carried over from page 21 Line: 4 on pg 22

EPA comment:

Chudhry and Wheeler, 1988

Aventis' response:

This reference is not included in the reference list

Mobility

Page: 22 Paragraph: 1 Line: 1

EPA comment:

Carbaryl is considered to be mobile to very mobile in soils.

Aventis' response:

See response directly below.

Page: 22 Paragraph: 3 Line: 1-2

EPA comment:

Based on batch equilibrium experiments (*MRID* 43259301) carbaryl was determined to be very mobile to mobile in soils.

Aventis' response:

The classification of carbaryl as mobile to very mobile is inconsistent with measured K_{oc} values of 177 to 249. According to the widely used classification scheme of McCall, *et al.* (1980) wherein K_{oc} values between 150 and 500 denote medium mobility in soil, carbaryl would be classified as having medium mobility in most soils. This classification of medium mobility is further supported by the acceptable column leaching study (MRID 43320701) in which aged carbaryl residues were only slightly mobile in a number of soils. The mobility of carbaryl would be expected to be higher in sandy soils or in soils of low organic matter.

Field Dissipation

Page: 22 Paragraph: 5 Line: 3

EPA comment:

The submitted field and aquatic dissipation studies were determined to be unacceptable, and did not provide useful information on movement and dissipation of carbaryl or its degradation products.

Aventis' response:

The field dissipation study (MRID 41982605) submitted in 1991 demonstrated that carbaryl dissipated very rapidly ($t_{1/2}$ < 1 week) with no measurable leaching. The study included two sites, one in North Carolina and one in California. At the North Carolina site, ~ 95% of the Time 0 residues had dissipated by the first sampling period 7 days after application (the planned first sampling at 3 days was not collected due to rain). Similarly, ~ 85% of the Time 0 residues had dissipated by 7 days after application at the California site. Concerning the movement of carbaryl, samples were taken to a depth of 0.9 meters in increments of 0.15 meters. No residues were found below the upper 0.15 meters.

Page: 23 Paragraph: 3 Line: 2

EPA comment:

Because of inappropriate sampling intervals, poor sample storage stability, lack of degradate monitoring, rainfall and irrigation that were less than evapotranspiration, and irrigation water with high pH, these studies do not provide reliable information on the rate of dissipation of parent carbaryl or formation of degradation products.

Aventis' response:

- The estimated half-life determined from this study was < 3 days. Sampling at intervals such that several sampling events are taken prior to the half-life of the product is impractical for rapidly degrading chemicals (e.g., those with half-lives less than a week). For this rapidly degrading chemical an estimate of the half-life should be sufficient for risk assessments even if it is not precise.
- After the report was submitted to California, the freezer storage stability recoveries at six and nine months were measured but not reported. Rainfall plus irrigation approximated an inch a week and was more than enough to maintain a good soil moisture for agricultural purposes.
- Sulfuric acid is routinely added to irrigation water in the region of California where the field test was conducted to neutralize the water's high pH. Although not stated in the report, the irrigation water in the California trial was treated in the typical commercial fashion. The acid is injected into the irrigation pipe as water is pumped through it. Unfortunately, the pH of the water arriving at the field after treatment was not measured.

Aquatic Field Dissipation

Page: 24 Paragraph: 2 Line: 3

EPA comment:

They (do) not provide useable information on the dissipation of carbaryl and 1-naphthol in aquatic field conditions.

Aventis' response:

- The soil metabolism study referred to in the report found that the total water soluble metabolites did not exceed 5% of the total radioactive residue, the primary hydrolysis product, 1-naphthol, was not found, and that the only analyte of concern was the parent insecticide, carbaryl. A soil metabolism study reviewed concurrently by the Agency was issued later (MRID 42785101, classified “acceptable”) with similar results. Although the major soil metabolite, 1-naphthol, was found at significant levels at day 0 and day 1, the levels were less than 0.7% by day 4 and non-detectable by day 14. Two other metabolites were identified but never exceeded levels of 1.7% of the total residue. Again the only residue of concern was the parent insecticide, carbaryl.

- If present, 1-naphthol would have been detected by the residue method used to measure the residues of carbaryl in the soil.

- The estimated half-life determined from this study was < 2 days. Sampling at intervals such that several sampling events are taken prior to the half-life of the product is impractical for rapidly degrading chemicals (e.g. those with half-lives less than a week).

Page: 24 Paragraph: 2 Line: 4

EPA comment:

Frozen storage stability data were provided for only 6 months, although the water samples were stored for up to 14 months and the soil samples were stored for up to 17.5 months prior to analysis. The data suggest that carbaryl and 1-naphthol degraded significantly during storage. In the six months of storage carbaryl degraded an average of 34 % in Texas water and 39% in from Mississippi. 1-naphthol degraded 50% in water from Texas and 69% from Mississippi. Degradation did not appear linear, and it is not possible to extrapolate out to 14 months. It was therefore not possible to evaluate the actual concentrations of carbaryl and 1-naphthol in the samples or estimate the dissipation rates.

Aventis' response:

The existing 6-month storage stability provides sufficient information to calculate the concentrations of carbaryl in the samples. However, the metabolite 1-naphthol was shown to degrade significantly under the same freezer conditions. This instability simply confirms that 1-naphthol's presence in the environment would be very limited and should not be of concern.

Foliar Dissipation

Page:24 Paragraph: Last

EPA comment:

The reported rates of carbaryl dissipation from foliar surfaces varies from 1 days to 30 days. In their review of literature data on pesticide foliar persistence, Willis and McDowell (1987) report that carbaryl dissipation rates varied from 1.2 to 29.5 days… For terrestrial risk assessment modeling EFED used 35 days…

Aventis' response:

As stated in comments to Table 3, the foliar dissipation half-life used by EFED for terrestrial risk assessment is too long and should be corrected. Table IV of the Willis and McDowell review lists 10 foliar half-lives for various formulations of carbaryl applied to different crops. Five of these half-lives are for a study designed to evaluate a new analytical procedure for measuring carbaryl residues on plants. This study was conducted on plants grown in a greenhouse, with some of them receiving an unknown amount of simulated rainfall. These studies on greenhouse-grown plants should not be used to evaluate foliar persistence in the field. The foliar persistence of pesticides can be considerably different for residues on and in plants grown in greenhouses versus the field. Eliminating the half-lives for the greenhouse-grown plants results in the following

half-lives for carbaryl on field plants: Cotton, 1.2, 1.3, 1.5 days; strawberry, 4.1 days; tomato 1.4 days. Therefore, the longest half-life of 4.1 days should be used for terrestrial risk assessment modeling.

Aventis will conduct a more thorough review of the data on the foliar dissipation of carbaryl and prepare a more detailed response during the 60-day public comment period.

Atmospheric Transport

Page: 25 Paragraph: 1 Line: 2

EPA comment:

Waite, *et al.*, 1995

Aventis' response:

This reference is not included in the reference list

Page: 25 Paragraph: 1 Line: 3

EPA comment:

Beyer *et al.*, (1995)

Aventis' response:

This reference is not included in the reference list

Page: 25 Paragraph: 3 Line: 5

EPA comment:

Schomburg *et al.* (1991)

Aventis' response:

This reference is not included in the reference list

1-Naphthol Fate and Transport

Page: 26 Paragraph: 2 Line: 1-2

EPA comment:

In an aerobic soil metabolism study (MRID 42785101), 1-naphthol degraded rapidly to non-detectable levels within 14 days.

Aventis' response:

The data from this study demonstrate that under aerobic soil conditions the formation and decline of 1-naphthol, starting from parent carbaryl, is complete in less than 14 days. The study data show an average maximum 1-naphthol level of 34.5% of applied carbaryl by day 1, declining to 2.8% by day 2, 0% by day 4, 0.2% by day 7 and 0% at day 14. These data suggest a preliminary half-life of less than 1 day for the major degradate 1-naphthol. This half-life can be used for preliminary environmental fate modeling to estimate EECs for 1-naphthol.

Page: 26 Paragraph: 3 Line: 1

EPA comment:

No guideline information was submitted on 1-naphthol sorption. Literature information suggests that it is not strongly sorbed.

Aventis' response:

The statement suggesting that 1-naphthol is not strongly sorbed to soil should be deleted. In support of the 1-naphthol sorption statement the Agency has cited only one paper by Karthikeyan *et al.* (1999) that was conducted using aluminum hydroxide as the sorbent. Soil is composed of much more than aluminum hydroxide, so this study is more of a mechanistic description of sorption to this one component of soil and not a study of sorption to soil as a whole. This cited study reported that 1-naphthol does not show significant sorption to aluminum hydroxide when allowed to sorb for 20 hours in the dark in the absence of oxygen. However, there was a significant increase in sorption with increasing equilibration time, and as the Agency stated, the increase is influenced by pH, as would be expected for an acidic phenolic compound.

Additional information available in the literature demonstrates that the sorption of 1-naphthol to soil is stronger than that seen for carbaryl itself. Hassett *et al.* (1981) have demonstrated that the sorption of 1-naphthol was the result of sorption to organic carbon resulting in an average K_{oc} of 431 ± 40 for 10 of the 16 soil samples they tested. In the remaining 6 soil samples the K_{oc} was even higher (1,645 to 15,618). Hassett *et al.* (reference submitted as part of 30-day response document) hypothesized that the higher K_{oc}s in these 6 soils, in which the organic carbon to clay ratio was very low, the clay surfaces were more accessible and the sorption of 1-naphthol was apparently controlled by the clay fraction. In Burgos *et al.* (1999), cited by EPA elsewhere in the RED, it was shown that there is significant sorption of 1-naphthol to two sandy soils, and that oxidative coupling reactions were responsible for the strongly bound portion. In an earlier paper by Burgos *et al.* (1996) it was shown that both biologically-mediated and soil-catalyzed oxidative coupling lead to significant binding of 1-naphthol residues to soil. These data indicate that 1-naphthol is less mobile and less susceptible to leaching than carbaryl itself, and they demonstrate that at least a portion of the 1-naphthol residue is tightly sorbed to soil constituents.

To meet the requirement by the Agency for information on the adsorption and desorption of 1-naphthol, the registrant is conducting an adsorption/desorption study to meet the

163-1 guideline. Study results should be available for submission to the Agency in the first quarter of the calendar year 2002.

Aquatic Exposure Assessment

Surface Water

Page: 26 Paragraph 4 Line 1

EPA comment:

Five crop scenarios: apples, field corn, sweet corn, oranges and sweet potatoes scenarios were use in modeling for surface water EEC.

Aventis' response:

The fifth crop modeled was sugar beets (not sweet potatoes).

Page: 27 Table 4

EPA comment:

Hydrolysis half-life at pH 9 stated to be 5 hours.

Aventis' response:

The study results, and the summary of the study presented on page 20, show the correct half-life at pH 9 to be 3.2 hours.

Page: 27 Table 4

EPA comment:

(K_{oc} = 211 for SCIGROW)

Aventis' response:

This is the mean K_{oc}. According to EPA guidance the median K_{oc} (209) should be used for SCI-GROW, although this difference would not be expected to affect the model results.

Pages: 27-28 Table 5

EPA comment:

Tier II surface water estimated environmental concentration (EEC) values derived from PRZM/EXAMS modeling for use in ecorisk assessment (calculated using standard pond.)

Aventis' response:

The PRZM input tables were not provided for the standard pond scenarios, so the assumption is made that the same application methods were used for the standard pond as for the Index Reservoir scenarios that were provided as an electronic copy of a draft of Appendix B.

It would be of benefit for the Agency to state which of the carbaryl labels were used to develop the "maximum" label application rate scenarios. It would be useful to add another column to this table to specify which method of application was used to generate the EECs rather than the generic "air/ground" in column 1. There are a number of errors in the input parameters (noted below) that would lead to changes in the calculated EECs and therefore the risk quotients for these uses.

If the modeling for the "average" scenarios were conducted using aerial applications for citrus and apples (as was the case for the Index Reservoir scenarios), then the model results over-estimate the contributions from spray drift. Few applications to these crops are made aerially. Therefore, the model results over-estimate the contributions from spray drift since the "average" applications to these crops are made using ground airblast equipment with a spray drift of 6.3% in the model versus aerial applications with a spray drift of 16%.

The "average" scenario for sweet corn in Ohio should be 3 applications at 1.1 lb. ai/A/application (as noted in the memo, "Average application rate from Quantitative Usage Analysis for Carbaryl, prepared July 21, 1998 by Frank Hernandez, OPP/BEAD") and not the 2 applications at 3.4 lb. ai/A/application as listed in the table. It should be noted that the "average" scenario presented in this table, 2 applications per year at 3.4 lb. ai per application, exceed the maximum rate allowed on the label.

The maximum label rate application scenario for apples that is allowed by the Sevin brand XLR PLUS label (E.P.A. Reg. No 264-333), the Sevin brand 80WSP and CHIPCO Sevin brand 80WSP labels (E.P.A. Reg. No 264-526) and the CHIPCO Sevin brand SL label (E.P.A. Reg. No 264-335) is 5 applications at 3 lb. ai/A/application made every 14 days. The scenario used in the model applies less than the maximum amount of product allowed by the labels. In addition, if the same application timing was used in the modeling for the standard pond scenario as was used in the index reservoir scenario (applications made by air every 4 days) this would be a violation of the Aventis labels which restrict applications to a minimum of every 14 days.

The "average" scenario for sugar beets in Minnesota should be 1 application at 1.3 lb. ai/A/application (as noted in the memo, "Average application rate from Quantitative Usage Analysis for Carbaryl, prepared July 21, 1998 by Frank Hernandez, OPP/BEAD") and not 1 application at 1.5 lb. ai/A/application as listed in the table.

The "Citrus" scenario would be more appropriately labeled Oranges. For the average scenario, the 3.4 lb. ai/A/application rate listed in Table 5 is for oranges (as noted in the memo, "Average application rate from Quantitative Usage Analysis for Carbaryl, prepared July 21, 1998 by Frank Hernandez, OPP/BEAD"), which is the highest "average" application rate for any type of citrus. Therefore, this "average" scenario for oranges are at the high end for all citrus and overestimates the PRZM/EXAMS derived EECs for use in the other citrus crops. "Average" application rates for other citrus as listed in the memo are:

Lemons – 1.3 applications at 2.7 lb ai/A/appl
Grapefruit – 1.6 applications at 1.4 lb ai/A/appl
Citrus, other – 1.8 applications at 1.8 lb ai/A/appl

The maximum label application rate for citrus is 7.5 lb ai per application, not 5 lb ai, with a maximum of 20 lb ai total allowed per year. In California only, a single application is allowed at the rate of 5 to 16 lb ai per season for control of California red scale and yellow scale.

Estimated Environmental Concentrations for Terrestrial Ecological Risk Assessment

Page: 29 Paragraph: 2 Line:2-4

EPA comment:

In the absence of reliable foliar dissipation data a dissipation half-life of 35 days is used. Published literature shows that carbaryl dissipation rates vary, and are among the highest observed for any pesticide (Willis and McDowell, 1987).

Aventis' response:

As stated in more detail above, some of the foliar dissipation half-lives listed in this reference are high because they were generated in the greenhouse, not in the field, and therefore they should not be used. Eliminating the half-lives for the greenhouse-grown plants results in the following half-lives for carbaryl on field plants: Cotton, 1.2, 1.3, 1.5 days; strawberry, 4.1 days; tomato 1.4 days. Therefore, the longest half-life of 4.1 days should be used for terrestrial risk assessment modeling.

Page: 29 Paragraph: 2 Line:6

EPA comment:

A more thorough description of the model calculations and ELL-FATE outputs are attached in Appendix B.

Aventis' response:

No such description or attachments were provided, so Aventis did not have the opportunity to evaluate the model.

Page: 29 Paragraph: 2 Line:last

EPA comment:

…Tables 4,7, 8 and 9, Appendix D.

Aventis' response:

These tables are in Appendix C.

5.0 Drinking Water Assessment

Water Resources Assessment

Page: 29 Paragraph: 3 Line:3

EPA comment:

Carbaryl tends not to partition to soil, aquifer solids, or sediment.

Aventis' response:

This sentence is misleading and should be reworded. Carbaryl does partition onto these sorbents, but the sorption coefficients are not high. Suggest rewording this such as: "Carbaryl tends not to bind tightly to soil, aquifer solids, or sediment."

Page: 29 Paragraph: 4

EPA comment:

Under certain conditions carbaryl can be expected to persist in the environment. Under low pH conditions the compound is stable to hydrolysis. In anaerobic environments metabolism is fairly slow ($t_{½}$ = 72 days). This suggests that carbaryl may leach to ground water and persist in some aquifers.

Aventis' response:

This last statement should be removed. In contrast to this hypothesis are the data presented in the NAWQA and EPA databases that demonstrate that carbaryl is not likely to leach to ground water and is not likely to persist in aquifers. The fact that carbaryl has been widely used in agricultural and urban settings for more than 35 years, and yet is found at concentrations greater than 0.1 µg /L in only 0.027% of the agricultural wells, urban wells and aquifers sampled by NAWQA (Kolpin, 2001), indicates that this statement has little merit. Furthermore, the last sentence is in direct contradiction to the statement made at the beginning of the preceding paragraph that carbaryl "…has limited potential to leach to ground water."

Page: 30 Paragraph: 1 Lines 1-3

EPA comment:

Surface water monitoring studies show that carbaryl is the second most widely detected insecticide after diazinon. Carbaryl, at typically low concentrations, is found in greater than 20 % of surface samples at concentrations up to 7 ppb.

Aventis' response:

These summary statements are based on the NAWQA database, with the exception of the 7 ppb concentration. The highest reported value in the NAWQA database is 5.5 ppb. The value of 7 ppb does not come from the NAWQA database but from the report by Werner *et al*. (2000). In fact, a maximum carbaryl concentration of 8.4 ppb was reported for surface water samples in the California DPR surface water database (see discussion section). The sources of the information should not be mixed, or the source of the information should be explicitly stated.

Drinking Water Exposure Assessment

Page: 30 Paragraph: 2 Line:3-4

EPA comment:

Carbaryl is the second most commonly detected insecticide in surface water, and can be expected to contaminate drinking water derived from surface water bodies.

Aventis' response:

The surface water-monitoring program conducted by Aventis shows an insignificant impact of carbaryl on drinking water.

Page: 30 Paragraph: 2 Line: 7

EPA comment:

The maximum reported value was 7.0 µg /L.

Aventis' response:

The maximum value reported in the NAWQA database is 5.5 µg /L. The only carbaryl detection reported in the study by Werner *et al*. (2000) was 7.0 µg /L. The maximum value reported in the California DPR Surface Water database is 8.4 µg /L. Since all of the statistics made in this paragraph refer to the NAWQA data, the reference to the maximum reported concentration should be 5.5 µg /L.

Page: 30 Paragraph: 4 Line: 2

EPA comment:

Older studies using GC or GC/MS generally have poor recovery and quantitation limits. Because of this difficulty in analysis the actual concentration of carbaryl in groundwater and surface waters may be higher than reported.

Aventis' response:

The basis for making this generalization is not readily apparent and these statements should be removed. Comments regarding the recovery reported for the GC/MS method used in the NAWQA survey are made below in reference to statements made on page 34 paragraph 5, and are elucidated in the discussion section at the end of this response document. The method detection limit (MDL) reported for the GC/MS method used for the NAWQA program is 0.003 ppb (Zaugg *et al*., 1995; Larson *et al.* , 1999). The limit of detection for the HPLC/MS/MS method used in the carbaryl surface water monitoring study being conducted by the registrant (LOD, 0.002 ppb; LOQ 0.030 ppb) is similar to the GC/MS method used for the NAWQA program. In addition to the GC/MS method used in the NAWQA program, carbaryl was also analyzed by HPLC/photodiode-array detection in a limited number of samples with a MDL of 0.008 (Werner *et al*., 1996). Therefore, the quantification limits reported for the GC/MS method used to generate a majority of the carbaryl data in the NAWQA database is very similar to the quantification limits for available HPLC methods. See the discussion section at the end

of this response document for a summary of the available NAWQA data obtained by the GC/MS and HPLC/PDA methods.

Page: 30 Paragraph: 4 Line: 4

EPA comment:

More recent studies using HPLC/MS should provide better data on the true extent and magnitude of water contamination from the use of carbaryl.

Aventis' response:

Aventis believes that our ongoing targeted surface water-monitoring program using HPLC/MS/MS accurately reflects the extent and magnitude of carbaryl exposure in drinking water derived from surface water.

Drinking Water Modeling

Page: 31 Paragraph: carried over from page 30 Line: 8

EPA comment:

A partial list of input parameters for the PRZM/EXAMS modeling are given in Table 4.

Aventis' response:

The partial list of input parameters in Table 4 includes multiple conservative assumptions likely to lead to significant over-estimation of the potential surface water concentrations of carbaryl.

Page: 31 Paragraph: 2 Line: 1

EPA comment:

For the Index Reservoir scenario using maximum label rates, acute EEC values ranged from about 10 µg/L from sugar beets to about 500 µg/L from citrus (Table 6).

Aventis' response:

Table 6 on page 33 shows a concentration of 19 µg/L for sugar beets treated with the maximum label rate of 2 x 1.5 lb ai, not 10 as stated in this sentence. A low EEC value of 9 µg/L for sugar beets results from the "maximum reported" application scenario of 1 x 1.2 lb ai/A.

Page: 31 Paragraph: 2 Line: 3

EPA comment:

Chronic EECs ranged from about 1 to 28 µg/L.

Aventis' response:

Table 6 on page 33 shows that this is correct when considering all of the model scenarios. However, either the same maximum label rate reference should be used as in the preceding sentence (in which case the minimum chronic EEC would be 2), or the basis for the preceding sentence should be changed from the maximum label rate to include all application scenarios to keep the comparisons consistent.

Page: 31 Paragraph: 2 Line: 6

EPA comment:

It is highly unlikely that any but the most extensive targeted monitoring would capture the actual peak concentrations.

Aventis' response:

The role of a peak concentration in dietary exposure assessment is undergoing re-examination within EPA. The current policy of EPA appears to define a certain percentile as an appropriate value for use in screening assessments, but the exact percentile to be used is being currently set by EPA management. (The most recent documents from EPA cite the 95^{th} or 99^{th} percentile.) For more comprehensive assessments, a distribution of values is preferred.

Page: 31 Paragraph: 2 Line: 7

EPA comment:

The results of the modeling provide a conservative, though not unreasonable, estimate on possible concentrations drinking water.(sic)

Aventis' response:

The modeling, performed according to EPA procedures, provides an upper bound estimate on potential concentrations in drinking water from surface water. Whether the modeling estimates are reasonable depends on the specific assumptions. For carbaryl, the three-year monitoring program (conducted according to EPA and ILSI guidance available at the time the study was started) shows that the model calculations are unreasonable. These conservative assumptions include a 3x factor on both the aerobic soil and aerobic aquatic half lives, assuming the maximum drift rate for aerial applications throughout the county (in Florida citrus almost all applications are by air blast with ground equipment), and the application rate over a watershed. The conservative nature of the application assumption alone probably results in an overprediction by at least two orders of magnitude. The modeling calculations assume an application rate of 17.4 lbs/acre of watershed annually. In Hardee County, the county with the highest usage of carbaryl, the average use rate on a countywide basis is only 0.31 lb/acre (See Appendix II). In Manatee County, the county with the highest usage containing a watershed used to supply drinking water, the average rate on a countywide basis is 0.027 lb/acre.

Page: 31 Paragraph: 2 Line: 8

EPA comment:

A more detailed assessment of the source of water used to provide drinking water and the relationship between the areas where carbaryl is used and surface water sources is required to more accurately evaluate possible human exposures.

Aventis' response:

As mentioned by EPA in this document, ground water is the source of the majority of Florida drinking water. Many of the counties with the highest use of carbaryl contain no watersheds used to provide drinking water. As discussed more fully in Appendix I, the watershed supplying the Manatee County Water Treatment Plant appears to have the most carbaryl usage of drinking water watersheds in Florida.

Water Treatment Effects

Page: 31 Paragraph: 3 Line: 8

EPA comment:

Since relatively (sic) few water treatment facilities in the U.S. use ozone the limited data available do not indicate that carbaryl is likely to be degraded in the majority of treatment plants.

Aventis' response:

The monitoring program conducted by the registrant shows that removal occurs in some treatment plants. The effect of treatment seemed to be greater in systems using carbon treatment.

Page: 33 Table 6

EPA comment:

Drinking Water EECs

Aventis' response:

Many of the comments for this table are similar to those for the EECs for ecological risk found in Table 5.

The PRZM model input parameters for the Index Reservoir scenarios were received as an electronic copy of a draft of Appendix B. These input files are very useful for assessing the scenarios that have been modeled.

It would be useful to add another column to Table 6 to specify which method of application was used to generate the EECs (and thus the application efficiency and spray drift values). It would be of benefit for the Agency to state which of the carbaryl labels were used to develop the "maximum" label application rate scenarios. There are a number of errors in the input parameters (noted below) that would lead to changes in the calculated EECs and therefore the risk quotients for these uses.

The model parameters listed in the electronic draft of Appendix B show that the "average" scenarios for citrus and apples were conducted using aerial applications. Few applications to these crops are made aerially. Therefore, the model results over-estimate the contributions from spray drift since the "average" applications to these crops are made using ground airblast equipment with a spray drift of 6.3% versus aerial applications with a spray drift of 16%.

The "maximum label rate" application scenario for apples that is allowed by the Sevin brand XLR PLUS label (E.P.A. Reg. No 264-333), the Sevin brand 80WSP and CHIPCO Sevin brand 80WSP labels (E.P.A. Reg. No 264-526) and the CHIPCO Sevin brand SL label (E.P.A. Reg. No 264-335) is 5 applications at 3 lb ai/A/application made every 14 days. The scenario used in the model applies less than the maximum amount of product allowed by the labels. In addition, application timing was used in the modeling for the index reservoir scenario (applications made by air every 4 days) that would be a violation of the Aventis labels which restrict applications to a minimum of every 14 days.

The "average" scenario for sweet corn in Ohio should be 3 applications at 1.1 lb ai/A/application (as noted in the memo, "Average application rate from Quantitative Usage Analysis for Carbaryl, prepared July 21, 1998 by Frank Hernandez, OPP/BEAD") and not the 2 applications at 3.4 lb ai/A/application as listed in the table. The PRZM input file shows the correct inputs of 3 applications at 1.1 lb ai/A/application.

The "average" scenario for sugar beets in Minnesota should be 1 application at 1.3 lb ai/A/application (as noted in the memo, "Average application rate from Quantitative Usage Analysis for Carbaryl, prepared July 21, 1998 by Frank Hernandez, OPP/BEAD") and not 1 application at 1.5 lb ai/A/application as listed in the table and the PRZM input file.

The "Citrus" scenario would be more appropriately labeled Oranges. For the average scenario, the 3.4 lb ai/A/application rate listed in Table 5 is for oranges (as noted in the memo, "Average application rate from Quantitative Usage Analysis for Carbaryl, prepared July 21, 1998 by Frank Hernandez, OPP/BEAD"), which is the highest "average" application rate for any type of citrus. Therefore, this "average" scenario for oranges is at the high end for all citrus and overestimates the EECs for use in the other citrus crops. "Average" application rates for other citrus as listed in the memo are:

Lemons – 1.3 applications at 2.7 lb ai/A/appl
Grapefruit – 1.6 applications at 1.4 lb ai/A/appl
Citrus, other – 1.8 applications at 1.8 lb ai/A/appl

Ground Water Resources

Page: 34 Paragraph: carried over from page 33 Line:3

EPA comment:

U.S. EPA. Pesticides in Groundwater Database (Jacoby *et al.*, 1992)

Aventis' response:

This reference is not provided in the reference list.

Page: 34 Paragraph: 3 Line: 3

EPA comment:

Detections were from (sic) mainly from three use sites: wheat (5.8 % of well samples from wheat land use), orchards and vineyards (1.7 % of well samples from orchard and vineyard land use), and urban (1.8% of urban groundwater samples).

Aventis' response:

Updated information (noted below) is not summarized in the same manner as in this statement, so direct comparisons cannot be made easily. However, the updated information indicates a similar pattern of low concentrations of carbaryl detections in a limited number of ground water resources.

Page: 34 Paragraph: 3 Line: 6

EPA comment:

Limitations in analytical methodology (described elsewhere) apply to groundwater sample analysis also suggesting that there (sic) actual maximum concentrations and extent of contamination may be significantly higher.

Aventis' response:

This statement is misleading and should be deleted. The validation of the most widely used GC/MS method for the data contained in NAWQA show recoveries of 86 to 94% at spiking levels of 0.1 to 1.0 µg/L with an MDL of 0.003 µg/L. The HPLC method validation reported recoveries of 58 to 64% % at spiking levels of 0.1 to 1.0 µg/L with an MDL of 0.018 µg/L. Furthermore, using the GC/MS method, a mean recovery of 115% was found for field matrix spikes of carbaryl at spiking levels of 0.1 µg/L. With the GC/MS method MDL of 0.003 µg/L and a mean recovery of 115% for the field matrix spikes, this method cannot reasonably be characterized as stated by EPA. Additional details of the method validations and field matrix spikes are provided in the 'Discussion Section' at the end of this response.

Page: 34 Paragraph: 3 Line: last

EPA comment:

…and updated information is available at: http://water.wr.usgs.gov/pnsp/ja/est32/.

Aventis' response:

This web page was last updated in 1998. A more recent update by Kolpin was posted June 11, 2001 at: http://water.wr.usgs.gov/pnsp/pestgw/ and is the source of the updated information included in the 'Discussion Section' at the end of this response.

Surface Water Resources

Monitoring Data

Page: 34 Paragraph: 4 Line:5-6

EPA comment:

Because of limitation in the analytical methods used there is some question as to the accuracy of carbaryl analysis.

Aventis' response:

This generalized statement needs to be qualified or deleted. Whereas the authors of reports written as part of the NAWQA program have been clear about the potential limitations of the quantitative nature of the carbaryl data in the database, they have also been clear about the validity of the qualitative nature of the data. The use of the multi-residue method in the NAWQA program does have some limitations as a result of the large numbers of diverse pesticides and degradation products that they are monitoring. However, the QC/QA data generated as part of the NAWQA program (described in the discussion section on surface water at the end of this response) demonstrate the validity of the detections of carbaryl in the studies. The monitoring study conducted by the registrant, and reported in this section, does not have the same potential limitations in the analytical method since the method is looking specifically for carbaryl. Therefore, the analytical method used by the registrant does not raise questions about the accuracy of the carbaryl analysis.

Page: 34 Paragraph: 4 Line:5-6

EPA comment:

Poor analytical methods probably have resulted in lower detection rates and lower concentrations than actually present.

Aventis' response:

This generalized statement should be deleted for reasons provided above and in the discussion section.

NAQWA (sic)

Change to NAWQA

Page: 34 - 35 Paragraph: 5 Lines: 5-8

EPA comment:

Carbaryl analytical results are fairly poor, with a typical mean percent recovery of 24% (σ = 15) in laboratory quality control samples, and a method detection limit (MDL) of 0.003 ug/L. This suggests that the values reported do not represent the maximum concentrations that exist, and that surface water contamination may be more widespread than the data show.

Aventis' response:

These statements are misleading and should be updated with further quality control data supplied by NAWQA.

A discussion of the analytical method used in the NAWQA program is presented in the USGS Open-File Report 95-181 (see Zaugg *et al*. (1995) in references). The mean percent recovery of 24% noted above can be found in Table 9 of this report and is by no means "typical". A mean recovery value of 24% was reported for reagent-grade water fortified at a level of 0.03µg/L with a method detection limit said to be 0.003 µg/L. Additional recoveries for fortified water samples (reagent-grade, ground and surface waters) ranged from 10 to 202% (see discussion section). The carbaryl data in the NAWQA database are amended with an "E" qualifier to indicate the variability found with this method, not because the carbaryl concentrations are underestimated.

Additional evaluations of field blank, field matrix spike and lab control spike samples as part of the NAWQA program can be found in a provisional report by Martin (1999). This report demonstrates the lack of detection of carbaryl in 100% of the field blanks, and median recoveries of 94.4% in 306 field matrix spikes and 93.0% in 1000 lab control spikes, each at spiking levels of 0.1 µg/L. These data suggest an adequate level of detection of carbaryl in the method used in the NAWQA survey of surface and ground water. See the additional discussion at the end of this document for further information regarding recoveries in spiked surface and ground water.

Page: 35 Paragraph: 2 Line: 7

EPA comment:

…at about 0.1 percent of the amount used in the basins (Larson *et al.*, 1999) http://water.wr.usgs.gov/pnsp/rep/wrir984222/load.html. The estimated carbaryl use on in agricultural applications is about 4 million pounds suggesting that 400,000 pounds are delivered to the nations streams draining agricultural areas.

Aventis' response:

This estimated use of carbaryl for agricultural applications over-estimates the use of carbaryl by about 1 million pounds. BEAD and USGS data cited on pages 6 and 7 are consistent with lower total pounds of carbaryl applied. In addition, 0.1 percent of 4 million pounds would be **4,000** pounds, not 400,000 pounds. If the 1987 – 1996 average of 2.5 million pounds carbaryl is used in the calculation, the total load suggested to be delivered to streams draining agricultural areas would be 2,500 pounds.

Registrant Monitoring Study

Page: 35 Paragraph: 4 Line: 11

EPA comment:

Carbaryl was analyzed by HPLC/MS with a limit of detection…

Aventis' response:

The analytical method used by the registrant in the surface water monitoring study uses tandem mass spectrometry (MS/MS) as the detection method. This type of detection involves quantification of "daughter" ions from a selected mass fragment and is more selective than an MS method. Therefore, to accurately reflect these differences, the method should be labeled as **HPLC/MS/MS**.

Page: 36 Paragraph: 3 Line: 9

EPA comment:

In several cases finished water had higher concentration than raw water, and finished water had detectable carbaryl when the raw did not. The highest concentration measured was in finished water (0.18 ppb). Raw water sampled at the same time had much lower concentration (0.010).

Aventis' response:

This statement is misleading and certainly does not consider the analytical uncertainty for concentrations below the level of quantification and near the level of detection. There were only two cases when finished water was greater than raw water when the concentrations in finished water were greater than 0.01 ppb (only one-third of the quantification limit). One case was when the raw water was 0.009 ppb and the finished water was 0.011 ppb. These two analyses are essentially equivalent, especially considering that they are only about a third of the quantification limit. The other case was at the Deerfield community water system. This drinking water facility uses a small river without a reservoir as a source for a small Community Water System. Farms are located immediately upstream of the facility. The intake is also not continuous (shut down over weekends). Therefore, getting a matching sample is quite difficult, especially for a short duration spike as a result of spray drift, summer thunderstorm, or perhaps a spill that almost immediately enters the river a runoff event. The rarity of this event is demonstrated by the absence of residues of this magnitude the next year (2000). Samples collected through this time of the year in 2001 also do not indicate a similar event. Although the data from this site cannot be used to determine the peak concentration, the data provide a distribution of residues through the three year period which will define up to the 99th percentile concentration of the distribution.

The Deerfield, Michigan community water system is one of the systems in which the greatest variability of residues would be expected. Most of the other community water systems are located on larger rivers, lakes, or reservoirs.

Because the design of study called for analysis of finished water only when there were residues in the raw water, there was only one finished sample analyzed when the raw water contained no residues. This sample was collected at the Deerfield community water system at the sampling interval after the finding of 0.16 ppb in the Deerfield system. The residue level in this sample was 0.004 ppb. The difference between 0.004 ppb and non-detect is insignificant, and if real can probably be attributed to water at much higher concentrations remaining in the system from the previous week.

Page: 36 Paragraph: 4 Line: 1

EPA comment:

Non-targeted monitoring, such as the NAWQA program, has shown much higher concentrations occur indicating that this study, while useful, can not be used to describe the overall distributions that occur throughout the entire use area.

Aventis' response:

The targets of the drinking water monitoring conducted by the registrant and the NAWQA program are different. The NAWQA program characterized surface water concentrations within a study area while the Aventis drinking water monitoring measured residues in inlets and outlets of drinking water facilities. Also the drinking water monitoring program considered only use areas with drinking water supplies. However,

for FQPA dietary assessments, the appropriate target is drinking water rather than surface water.

The main reason why the drinking water monitoring study did not show residues as high as in the NAWQA program is the location of the sampling points. Drinking water supplies tend to be located on larger surface water bodies than NAWQA sampling points (or in other words, the intakes for community water systems tend to be downstream of NAWQA sampling points). This additional time allows for additional degradation and dilution to occur. Finding the highest concentration at the Deerfield, Michigan system is not surprising since this intake is on one of the smallest surface water bodies included in the monitoring study (see response to Page: 36, Paragraph: 3, Line: 9 above for a more detailed explanation).

Page: 36 Paragraph: 4 Line: 4

EPA comment:

This study does not provide sufficient information to allow estimation of actual peak and mean concentrations that actually occur in all use areas.

Aventis' response:

Because most of the samples did not contain carbaryl residues, accurate estimates of the actual peak and mean concentrations can not be obtained. However, the distributions obtained from all sites can be used to define up to the 99th percentile concentration. The average cannot be accurately determined; however, the time-weighted average is only slightly above the limit of detection (and certainly less than 0.01 ppb) at all 20 sites.

The peak concentration in this study was measured at a community water system on a small river. The registrant agrees that the sampling schedule was not adequate to determine the true peak in such systems. Most of the other community water systems are located on larger rivers, lakes, or reservoirs. Therefore, the peak values are not likely to be an order of magnitude greater than the amounts present in the collected samples.

The distributions obtained in this study are suitable for use in dietary exposure assessments. When EPA policy establishes what percentile concentration is an appropriate regulatory endpoint, then these percentiles can be determined for each of the community water systems monitoring. These percentiles can then be compared with DWLOC values in screening assessments.

Page: 37 Paragraph: 2 Line: 1

EPA comment:

Only limited information was submitted on sampling site selection…

Aventis' response:

The summary in Appendix I of this response provides a description of the sites considered for the monitoring study and the rationale for the selection of the twenty sites. This information demonstrates that the community water systems selected for this study

are representative of the systems that are most likely to contain the highest concentrations of carbaryl residues.

Page: 37 Paragraph: 3 Line: 3

EPA comment:

This should include an explanation of why this study did not observe concentrations as high as those found in other, non-targeted studies, and how the results of this study can be related to concentrations that occur throughout the country.

Aventis' response:

The main reason why the drinking water monitoring study did not show residues as high as in the NAWQA program is the location of the sampling points. Drinking water supplies tend to be located on larger surface water bodies than NAWQA sampling points (or in other words, the intakes for community water systems tend to be downstream of NAWQA sampling points). This additional time allows for additional degradation and dilution to occur. Finding the highest concentration at the Deerfield, Michigan system is not surprising since this intake is on one of the smallest surface water bodies included in the monitoring study (see response to Page: 36, Paragraph: 3, Line: 9 above).

Since the drinking water study targeted drinking water systems in high-use watersheds, the data from this study are representative of the drinking water systems most likely to contain carbaryl.

Sacramento-San Joaquin River Delta

Page: 37 Paragraph: 4 Line: 4 - 5

EPA comment:

Carbaryl was found to be the sole causative agent at one of 20 sites…
The toxicity seemed to persist for several days…

Aventis' response:

The statement should be revised. The reference cited (Werner *et al*., 2000) lists carbaryl as "the primary toxicant" (not as the "sole causative agent"), even though an unknown was also found at the same time. No information about the "unknown" is provided. Both conclusions of "sole causative" and of "primary toxicant" cannot be substantiated without further evidence about the nature and concentration of the unknown. Actually, for another site the authors concluded about the unknown found there "*in 3 of 21 samples, toxicity observed could not be entirely explained by the identified primary toxicants.*" Additionally, it is at least questionable if the analytical method employed would detect all potential toxicants beside the insecticides it was set up for.

The toxicity seeming to persist is not explained or substantiated in the reference. The citation of such dubious results should be removed from the RED.

6.0 Hazard and Risk Assessment for Aquatic Organisms

Hazard assessment for Aquatic organisms

Estuarine/Marine Fish

Page:39 Paragraph: 2 Line: 6

EPA comment:

…carbaryl water concentration of 1.2 µg/ml…

Aventis' response:

To be consistent with the rest of the document the units should be presented in ppm ("carbaryl water concentration of 1.2 ppm")

Aquatic Plants

Page:40 Paragraph: 2 Line: 6

EPA comment:

Guideline 122-2 is not fulfilled.

Aventis' response:

The chapter should be revised. As detailed above (comments to Page 2 of the Memorandum), studies were submitted in 1992. The status for this requirement in an October 04, 2000 OPP Guideline Status Report (Chemical Review Management System) lists the guideline 122-2 status as "Acceptable/Satisfied".

Risk Assessment for Aquatic Organisms

Page:40 Paragraph: 4 Line: 3

EPA comment:

…corresponding levels of concern (LOCs) is presented in Appendix D.

Aventis' response:

The risk quotients are currently listed in Appendix C.

Estuarine/Marine Fish

Page:42 Paragraph: 1 Line: 17/18

EPA comment:

Chronic toxicity studies with an estuarine/marine fish species is required.

Aventis' response:

This requirement should be waived. Given the relatively short half-life of carbaryl in the aquatic environment and the low acute risk, it is unlikely that estuarine/marine fish species would be exposed to a chronic risk.

Page:42 Paragraph: 2 Line: 1

EPA comment:

There is one carbaryl use in particular that presents a major acute and chronic risk to estuarine/marine fish.

Aventis' response:

This sentence should be rephrased. While there might be an acute risk from the application to oyster beds, given that there is only one application every six years according to the reference cited by EPA, it is improbable that estuarine/marine fish would be exposed to a chronic risk.

7.0 Hazard and Risk Assessment for Terrestrial Organisms

Hazard Assessment for Terrestrial Organisms

Mammalian

Page:46 Paragraph: 4 Line: 1

EPA comment:

With a rat LD_{50} of 307 mg/kg…

Aventis' response:

Typographical error, the rat LD_{50} is 301 mg/kg.

Risk Assessment for Terrestrial Organisms

Avian Risk

Nongranular Formulations

Page:47 Paragraph: 4 Line: 5

EPA comment:

…levels of concern (LOCs) is presented in Appendix D.

Aventis' response:

The risk quotients are currently listed in Appendix C.

Page:48 Paragraph: 1 Line: 3

EPA comment:

… for 34 of 43 uses at maximum reported rates, and for 37 of 72 uses at "average" rates. (Appendix D, …

Aventis' response:

The risk quotients are currently listed in Appendix C.

Granular Formulations

Page:48 Paragraph: 2 Line: 5

EPA comment:

…for any of the granular carbaryl uses (Appendix D, Table 6).

Aventis' response:

The risk quotients are currently listed in Appendix C.

Mammalian Risk

Risk to Herbivores/Insectivores: Nongranular Formulations

Risk Quotients for Herbivores/Insectivores Based on Less than Maximum Label Use Rates

Page:48 Paragraph: 3 Line: 3 & 4

EPA comment:

… (Appendix D, Table 10a) and maximum reported (Doane data) use rates data available for 43 uses (Appendix D, Table 10b)

Aventis' response:

The risk quotients are currently listed in Appendix C.

Risk Quotients for Herbivores/Insectivores Based on Maximum Label Use Rates

Page:48 Paragraph: 6 Line: 1

EPA comment:

Carbaryl is moderately toxic to small mammals on an acute oral basis (rat LD_{50} = 307 mg/kg)

Aventis' response:

Typographical error, the rat LD_{50} is 301 mg/kg.
By using the lower LD_{50} all acute mammalian risk quotients will change slightly.

Page:49 Paragraph: 1 Line: 3

EPA comment:

…corresponding levels of concern (LOCs) is presented in Appendix D.

Aventis' response:

The risk quotients are currently listed in Appendix C.

Risk to Granivores: Nongranular Uses

Chronic risk: Nongranular Uses

Page:50 Paragraph: 2 Line: 8

EPA comment:

…summarized in Appendix D, Table 9.

Aventis' response:

The risk quotients are currently listed in Appendix C.

Reproduction Effects

Page:50 & 51 Paragraph: 4 / 1

EPA comment:

(Review of alleged reproduction effects of carbaryl).

Aventis' response:

The paragraphs should be changed. The literature cited in these paragraphs show ambivalent results. While some references seem to support the claim of reproductive effects, other references do not. The potential for reproductive effects in mammals was evaluated in the recently submitted 2-generation study in rats. No reproductive effects were seen in this guideline study. The NOAEC of 75 ppm was based on pup mortality.

Page:51 Paragraph: 4

EPA comment:

Feeding 2 or 20 mg/kg of carbaryl to pregnant rhesus monkeys (*Macacca mulatta*)

Aventis' response:

This paragraph should be deleted. As there are no native monkey species in the U.S., this reference is irrelevant for U.S. wildlife species. Additionally, the reference cited is only a brief abstract article consisting of one 17-line paragraph. Such information should not be the basis for use in a RED risk assessment.

9.0 References (non-MRID)

Some of the references cited in EPA's list are not full scientific articles, but only abstracts from meetings (e.g. DeNorsica, 1973; Doughtery et al. , 1971, Chapin et al. 1997). Such "publications" should not be used as references considered in risk assessments. Without a sufficient description of methods and a presentation of detailed results these studies cannot be evaluated to determine if the findings are or are not scientifically plausible. Similarly, at least three of the references (Gladenko *et al.* 1970, Krylova *et al.* 1975, Smirnov *et al.* 1971) cited as proof for reproductive toxicity are in Russian in Cyrillic writing making an appropriate and timely evaluation difficult. Due to the limited review time during the 30-day comment period, the registrant could not peruse all references. A more detailed response will be provided during the 60-day comment period.

Page: 59

EPA comment:

Carmel, R.F., Imhoff, J.C., Hummel, P.R., Cheplick, J.M. and Donigan, A.S., 1997.

Aventis' response:

The first name should be Car**s**el.

Page: 59

EPA comment:

Nkedi-Kizza and Brown (1988)

Aventis' response:

The date should be 19**9**8.

Appendix A: Environmental Fate Study Reviews (DERs)

Page:62 ff

EPA comment:

(Environmental fate DERs are included)

Aventis' response:

The DERs should not be included in the RED. Publication of DERs together with the RED is unusual and will put Aventis in a competitive disadvantage.

Appendix B: Refined Water Memo

EPA comment:

MEMO TO BE INSERTED WHEN APPROVED

Aventis' response:

This memo was provided as an electronic copy and needs to be inserted into the document. It included text that repeated several sections of the EFED document and it included PRZM input tables for the drinking water concentrations using the Index Reservoir scenario. It would have been of benefit to have the same PRZM inputs for the "standard pond" scenarios that were used to estimate surface water concentrations used in the aquatic risk assessments.

Appendix C: Ecological Risk Assessment

Toxicity Endpoints Used in the Risk Assessment

Page:129 (e-version)

EPA comment:		**Aventis' response**:
Mammalian acute oral LD50	rat = 307 mg/kg	The correct LD_{50} is 301 mg/kg
Mammalian chronic (reproduction) NOAEC	rat = 80 ppm	The result of the recently submitted 2-generation rat study should be used (75 ppm)

Avian Acute and Chronic Risk

Page:130 (e-version) Paragraph: 1 Line: 1

EPA comment:

Since the avian LC_{50} is greater than 5,000 ppm (Appendix E),

Aventis' response:

The toxicity data are currently listed in Appendix D.

Page:132 – 135 (e-version)

EPA comment:

(Acute Risk Quotients in Tables 4 and 5, as well as throughout the document were a reference is made to these quotients)

Aventis' response:

As the acute risk quotients are calculated on the basis of an LC_{50} of > 5000 ppm, the quotients should be given as "< (value)", not just the value. The values should also be changed accordingly throughout the document where a reference is made to these quotients.

Risk from Exposure to Non-granular Products

Page:137 – 147 (e-version)

EPA comment:

(Text and tables 7 - 10)

Aventis' response:

Text and tables should be revised. A rat LD_{50} of 307 mg/kg was used to calculate the acute risk quotients. The correct value is 301 mg/kg.
For calculation of the chronic risk quotient a NOAEC of 80 ppm was taken from a developmental study. The NOAEC of 75 ppm from a more relevant 2-generation rat study recently submitted should be used instead.

Risk from Exposure to Granular Products

Page:147 & 148 (e-version)

EPA comment:

(Text and Table 11)

Aventis' response:

Text and tables should be revised. A rat LD_{50} of 307 mg/kg was used to calculate the acute risk quotients. The correct value is 301 mg/kg.

Aquatic Plants

Page:152 (e-version)

EPA comment:

Based on a single core aquatic plant toxicity study available…
…recommended that toxicity studies with *Lemna gibba, Anabaena flos-aquae, Skeletonema costatum,* and a freshwater diatom be submitted.

Aventis' response:

The respective studies were submitted to the Agency in 1992 (see comments above to Page 2 of the Memorandum for a complete list and status).

Appendix D: Toxicity Assessment

Page:157 (e-version)

EPA comment:

Table 1 (spelling of author in MRID No. 00160000)

Aventis' response:

The author of MRID No. 00160000 should be "Hudson *et al.* ".
Also, it is not obvious why the same reference is one time classified "core" and six times "supplemental". The agency should reconsider if the use of a "supplemental" study (i.e., rock dove) in calculating all acute RQ values is justified.

Birds, Chronic Toxicity

Page: 158 (e-version) Paragraph: 3

EPA comment:

Bird kills attributed to carbaryl and involving blackbirds, ducks, starlings, grackles turkey, and cardinals have been reported in Pennsylvania, Virginia, New Jersey, North Carolina and Michigan (#1002048-001, #1000802-001, #1007720-020, ##1000799-003, #1004375-004).

Aventis' response:

The paragraph should be moved to the acute bird section.
Also, only individuals familiar with this information will recognize the numbers as the incident numbers from the EIIS database. An appropriate reference should be inserted here and in similar citations.

Page: 158 Paragraph: 1 Line: 2 & 3

EPA comment:

Exposure to carbaryl at levels equal to or greater than 1000 ppm in the mallard duck results in adverse reproduction effects, such as decrease in number of eggs produced include cracked eggs, fertility, embryonic mortality, and hatching success.

Aventis' response:

The sentence should be changed. The embryonic mortality and the hatching success were not different from the control.

Mammals, Acute and Chronic

Page: 158 & 159 (e-version)

EPA comment:

(rat LD_{50} of 307 mg/kg, NOAEC 80 ppm)

Aventis' response:

The acute LD_{50} value for rat should be corrected to 301 mg/kg, and the chronic NOEAC to 75 ppm from the 2-generation rat study.

Freshwater Fish, Acute

Page:161 (e-version)

EPA comment:

Table 6

Aventis' response:

The study classification of reference MRID 40098001 (Mayer & Ellersieck, 1986) should be reconsidered (and handled in a consistent fashion). A number of times the reference is classified "core", while in other instances the classification is "supplemental". The reference is an overview article with little description of test methods, analytical procedures, GLP, or study details. The results are generally listed in extensive tables (although summarized in the text for some chemicals). Such a review article cannot be regarded as a "core" study equivalent to the guideline studies that have to be prepared by registrants. Also, such studies with insufficient test method descriptions should not be used in a risk assessment as the primary source of information. A submission based on such data would have certainly been rejected by the Agency

Freshwater Invertebrates, Acute

Page:163 (e-version)

EPA comment:

Table 9

Aventis' response:

The study classification of reference MRID 40098001 (Mayer & Ellersieck, 1986) should be reconsidered (and handled in a consistent fashion). A number of times the reference is classified "core", while in other instances the classification is "supplemental". The reference is a review article with little description of test methods, analytical procedures, GLP, or study details. The results are generally listed in extensive tables (although summarized in the text for some chemicals). Such an overview article cannot be regarded as a "core" study equivalent to the guideline studies that have to be prepared by registrants. Also, such studies with insufficient test method descriptions should not be used in a risk assessment as the primary source of information.

Estuarine and Marine Invertebrates, Acute

Page:165 (e-version)

EPA comment:

Table 13, reference for glass shrimp: Mayer & Ellerersieck

Aventis' response:

The reference should be corrected in Mayer & Ellersieck.

Page:167 (e-version) Table 15

EPA comment:

Table 15, reference for MRID No. 00265665

Aventis' response:

The reference for MRID No. 00265665 should also contain the citation of an author.

DISCUSSION

1. Surface Water Concentrations

Summary of Registrant Surface Water/Drinking Water Monitoring Program

In section V, page 31 EPA states that the modeling simulations provide a conservative, though not unreasonable, estimate on possible concentrations in drinking water. The data from the registrant drinking water monitoring program provide the best estimate of concentrations of carbaryl in drinking water. This study uses the sampling design for acute endpoints recommended in industry/EPA meetings during 1999 (weekly sampling during times of peak concentrations over a three year period). Twenty sites representing the highest carbaryl use areas were selected based on the information provided in Appendix I. These included 16 sites in agricultural areas and 4 locations in urban areas. Samples were collected from the inlet and outlet water at each sampling interval. Outlet samples were only analyzed when residues were present in the inlet samples. The analytical method had a limit of quantification of 0.030 ppb and a limit of detection of 0.002 ppb.

Table 1 summarizes the results of the monitoring at each of the 20 community water systems. The maximum concentration observed was 0.16 ppb (average of four samples, the highest was 0.18 ppb) in a finished water sample from the Deerfield community water system located on the River Raisin in Lenawee County, Michigan. There were only five other samples above the limit of quantification of 0.030 ppb. One was a raw water sample containing 0.31 ppb from the Little Potato Slough Mutual community water system near Lodi in San Joaquin County, California (the source is the Little Potato Slough). The corresponding finished water sample was 0.007 ppb. A second one was a raw water sample in Brockton, MA which contained 0.031 ppb. No detectable residues were found in the corresponding finish water sample. The last three samples were from the Shades Mountain plant of the Birmingham community water system on the Cahaba River in Jefferson County, Alabama . Two were raw and finished samples of 0.038 and 0.032 ppb at the same sampling interval in 2001. . The other sample was 0.035 ppb in the raw water in a 2000 sample (the corresponding finished sample did not contain carbaryl residues.e. All residues were transient so the time weighted average concentration of carbaryl in each of the years was 0.005 ppb or less at all 20 community water systems.

Table 1. Summary of Results from the Carbaryl Drinking Water Monitoring Study.

Site	Major Uses	Maximum Concentration (ppt)						TWA Conc. (ppt)* in Outlet Water	
		Inlet Water			Outlet Water				
		1999	2000	2001**	1999	2000	2001**	1999	2000
Manatee, FL	citrus	9	3	ND	11	ND	NA	1	1
West Sacramento, CA	orchards, nuts	3	24	ND	3	10	NA	1	1
Lodi, CA	orchards, nuts	12	31	ND	4	7	NA	1	1
Riverside, CA	grapes, tree crops	8	ND	ND	ND	NA	NA	1	1
Lake Elsinore, CA	citrus	ND	3	6	NA	NA	Analysis Pending	1	1
Corona, CA	citrus	ND	ND	ND	NA	NA	NA	1	1
Beaumont, TX	various agricultural	ND	ND	ND	NA	NA	NA	1	1
Point Comfort, TX	rice, tree crops	18	5	ND	ND	ND	NA	1	1
Penn Yan, NY	grapes, apples	ND	23	ND	NA	ND	NA	1	1
Westfield, NY	grapes, apples	21	5	ND	ND	9	NA	1	1
Jefferson, OR	vegetables, strawberries	ND	10	ND	NA	ND	NA	1	1
Coweta, OK	pecans	4	ND	***	ND	NA	***	1	1
Pasco, WA	apples, potatoes	2	3	ND	ND	ND	NA	1	1
Manson, WA	apples	ND	ND	ND	NA	NA	NA	1	1
Deerfield, MI	vegetables	10	4	ND	160	ND	NA	5	1
Brockton, MA	cranberries	31	27	ND	ND	3	NA	1	1
East Point, GA	home and garden	18	18	4	3	8	ND	1	1
Midlothian, TX	home and garden	14	ND	14	ND	NA	ND	1	1
Cary, NC	home and garden	4	ND	ND	ND	NA	NA	1	1
Birmingham, AL	home and garden	23	35	38	ND	ND	32	1	1

* Annual Time Weighted Concentration, outlet values substituted for inlet values when available; values below the detection limit were considered to be half the detection limit.

** Results represent one to six months of sampling into the third year program.

*** No results available for the third year of sampling.

ND Not detected.
NA No outlet samples analyzed due to carbaryl residues not being detected in inlet samples.

Summary of Surface Water Data from the NAWQA Program

In Section 1 page 3, Section 4 page 28 and in Section 5 page 34, EPA has summarized the available surface water monitoring data from the NAWQA program as having detections in 46% of the 36 NAWQA study units between 1991 and 1998 with a maximum concentration of 5.5 ppb. The following tables summarize the carbaryl analyses presently available from this database.

Table 2 is a summary of the carbaryl detections in the updated database analysis recently reported by Larson (2001). This analysis was conducted only for samples collected during a one-year period of the most intensive sampling from each of the sampling sites. Numerous samples were excluded from this analysis as described by Larson:

> *"A few sites with sufficient sampling for pesticides were excluded from the analysis, in order to minimize bias caused by over-representation of a particular land use or agricultural setting. ... The sampling requirements for a site to be included in the analysis were a minimum of 8 samples collected in 6 or more months during the 1-year period. In addition, samples must have been collected during the expected period of elevated pesticide concentrations. At most of the sites used in this analysis, 20 to 30 samples were collected during the selected 1-year period.... Not all samples collected during the year at each site were used in the calculation of the summary statistics, however. Samples collected as part of a fixed-frequency sampling schedule were included, along with a much smaller number of samples collected during selected high or low flow conditions. Samples collected over a storm hydrograph, or as part of a study of diurnal variability, were excluded in order to avoid bias resulting from repeated sampling during extreme conditions. "*

Table 2.Carbaryl Detections Reported in Pesticides in Streams Update (Larson, 2001)

Site Type	Number of Sites	Number of Samples	Carbaryl Detection Frequency (%)				Maximum Estimated Concentration (µg/L)
			All	>=0.01 (µg/L)	>=0.05 (µg/L)	>=0.10 (µg/L)	
Agricultural Streams	62	1560	9.2	5.7	1.8	0.9	5.2
Urban Streams	22	611	43	37	19	12	3.2
Integrator[A]	31	595	15	11	2.7	1.2	0.43

[A] Large streams and rivers

Results in Table 3 and Table 4 show a breakdown of all the carbaryl analyses reported in the USGS NAWQA database, which was downloaded from their web site July 16, 2001. The data are reported separately for the GC/MS and HPLC/PDA analyses.

Table 3. Frequency of Carbaryl Detections by GC/MS in Different Concentration Ranges Reported in the NAWQA Database as of July 16, 2001

Land Use Type	Number of Samples	<=MDL[C]		>0.003 to 0.01		>0.01 to 0.1 ppb		>0.1 to 1 ppb		>1 ppb	
		No.	%	No.	%	No.	%	No.	%	No.	%
All Samples	10379	8388	80.82	617	5.94	1065	10.26	283	2.73	26	0.25
Agricultural	4349	3888	89.40	188	4.32	225	5.17	46	1.06	2	0.05
Urban	1763	921	52.24	161	9.13	463	26.26	195	11.06	23	1.30
Mixed[A]	3648	3022	82.84	247	6.77	345	9.46	33	0.90	1	0.03
Other[B]	619	557	89.98	21	3.39	32	5.17	9	1.45	0	0

[A] Large streams and rivers. Includes all of the "Integrator" sites listed in Larson, *et al.* ., 1999 and many more.
[B] Includes forest, rangeland, mining, etc.
[C] The method detection limit (MDL) for carbaryl analyzed by the GC/MS method is 0.003 µg/L, but updated MDLs presented in the database may be higher for some analyses and are included in this category.

Table 4. Frequency of Carbaryl Detections by LC/PDA in Different Concentration Ranges Reported in the NAWQA Database as of July 16, 2001

Land Use Type	Number of Samples	<=MDL[C]		>0.008 to 0.01		>0.01 to 0.1 ppb		>0.1 to 1 ppb		>1 ppb	
		No.	%	No.	%	No.	%	No.	%	No.	%
All Types	5516	5348	96.95	9	0.16	93	1.69	54	0.98	12	0.22
Agricultural	2528	2509	99.25	1	0.04	13	0.51	3	0.12	2	0.08
Urban	1189	1064	89.49	4	0.34	64	5.38	47	3.95	10	0.84
Mixed[A]	1523	1501	98.56	4	0.26	15	0.98	3	0.2	0	0
Other[B]	276	274	99.28	0	0	1	0.36	1	0.36	0	0

[A] Large streams and rivers. Includes all of the "Integrator" sites listed in Larson, *et al.* ., 1999 and many more.
[B] Includes forest, rangeland, mining, etc.
[C] The method detection limit (MDL) for carbaryl analyzed by the LC/PDA method is 0.008 µg/L, but updated MDLs presented in the database may be higher for some analyses and are included in this category.

Summary of Carbaryl Analytical Methods used in the NAWQA Program

In a number of instances throughout their review, EPA has made reference to the "poor recovery" for carbaryl noted in a NAWQA summary document (Larson, 1999). In this document, reference is made to mean percent recovery of 24% for carbaryl with a method detection limit (MDL) of 0.003 ppb. The Agency cites this low mean recovery several times as evidence that the concentrations of carbaryl reported in the database widely underestimate the actual concentrations of carbaryl in the water samples. This claim is misleading and should be removed from each location in the draft RED for reasons discussed below.

Two analytical methods were developed as part of the NAWQA program and both of them have been used in the analysis of carbaryl. The first method, used for a majority of the NAWQA data reported for carbaryl, is a GC/MS method with an MDL of 0.003 ppb (Zaugg, *et al.*, 1995). The second method, used for a limited number of samples in which carbaryl was analyzed, is an LC/Photodiode-Array (PDA) method with an MDL of 0.008 ppb (Werner *et al.* ., 1996). In the NAWQA database the quantitative data for carbaryl determined by the GC/MS method are flagged with an "E", as are data for several other analytes, indicating that the analysts have noted "the potential for variable performance" in the analysis of carbaryl. None of the carbaryl data in the NAWQA database has been corrected for procedural recoveries that were noted in the documents described above. Both of these methods are discussed below in relation to the recoveries found for the methods and the potential impact this could have on the analytical data for carbaryl.

Gas Chromatography/Mass Spectroscopy Method

The analytical method most used in the NAWQA program for the analysis of carbaryl in water samples is the GC/MS method described by Zaugg, *et al*., 1995. In this multi-residue method, the analytes are first removed from the water sample by sorption on a C-18 solid phase and are subsequently eluted from the solid phase, separated by GC and quantified by mass spectroscopy with selected ion monitoring. The identity of each analyte is confirmed by the appropriate combination of retention time and the ratios of three mass ions that are characteristic for the analyte.

> The recoveries for carbaryl spiked at different levels into three different types of water and analyzed by the GC/MS method are shown in Table 5 Mean percent recoveries of 151 and 202% were found for carbaryl fortified at 0.1 and 1.0 μg/L in reagent grade water. A preliminary MDL of 0.046 μg/L was calculated for the 0.1 μg/L spiking level. Mean percent recoveries of 10 and 75% were found for carbaryl fortified at 0.1 and 1.0 μg/L in a surface water sample collected from the South Platte River. However, carbaryl was detected at 0.18 μg/L in this water, or nearly twice the low spike level, raising questions about the validity of this result. Mean percent recoveries of 94 and 86% were found for carbaryl fortified at 0.1 and 1.0 μg/L in a ground water sample collected from a well in Denver. A mean recovery value of 24% was reported for reagent-grade water fortified at a level of 0.03 μg/L with a method detection limit calculated at 0.003 μg/L.

Table 5. Recovery and Precision for Multiple Determinations of Carbaryl in GC/MS Method for Carbaryl Spiked in Different Water Samples

Water type	Spike Concentration (μg/L)	Mean Recovery (%)	MDL Calculated
Reagent Grade	0.1	151	0.046
Reagent Grade	1.0	202	-
Surface[A]	0.1	10	-
Surface[A]	1.0	75	-
Ground[B]	0.1	94	-
Ground[B]	1.0	86	-
Reagent Grade	0.03	24	0.003

[A] Surface water was collected from the South Platte River near Henderson, Colorado. This water was found to contain significant concentrations of several pesticides including 0.18 μg/L carbaryl. This concentration was subtracted from the values determined to give corrected results.
[B] Ground water was collected from the Denver Federal Center Well 15.

Whereas the values reported by Zaugg, *et al*. (1995) are of interest in validating the analytical method, they are not as useful in evaluating the validity of the data contained in the NAWQA database. Therefore, quoting the mean recovery value of 24% for reagent grade water spiked with carbaryl at 0.03 μg/L as evidence that the concentrations reported in the database underestimate the actual concentrations of carbaryl present in the water samples is misleading. A more useful measure of the validity of the values in the database lies with the quality control checks that have been incorporated into the analysis of samples in the NAWQA program.

In a preliminary report, Martin (1999) reported the quality control data collected as part of the NAWQA surface and ground water programs by the 1991 NAWQA Study Unit teams or the National Water Quality Laboratory (NWQL) during 1992 to 1996. The data that were compiled includes field blanks, laboratory control spikes and field matrix spikes, which are defined below by Martin.

> *"Field blanks were collected at the field site with pesticide-grade blank water and are exposed to the field and laboratory environments and equipment similarly to environmental samples. Field blanks measure the frequency and magnitude of contamination (one type of positive bias) in environmental water samples from sources in the field and/or laboratory. Contamination is the main cause of false-positive detections (detecting a pesticide in a sample when, in truth, it is absent)."*

> *"Laboratory control spikes measure the bias and variability of the analytical method at a particular concentration. One laboratory control spike is measured in each analytical set of environmental samples. The laboratory control spike has*

the target pesticides spiked into pesticide-grade blank water at the laboratory and extracted, processed, and analyzed like environmental samples. Laboratory control spikes analyzed by GCMS were spiked at 0.1 μg/L…"

"Field matrix spikes measure the bias and variability of the analytical method PLUS any potential effects caused by (1) degradation of pesticides during shipment to the laboratory, (2) inferences in the determination of pesticides from unusual characteristics of the environmental water sample ("matrix effects"), and (3) other chemical processes that cause bias or variability in the measurements of pesticides in environmental water samples. Field matrix spikes analyzed by GCMS were spiked at 0.1 μg/L,…"

All of the carbaryl analyses in the field blanks, field matrix spikes and lab control spikes were conducted following the same method described by Zaugg *et al*., 1995 that was used to generate a majority of the carbaryl data contained in the NAWQA database. The data below were excerpted from Tables 1 to 4 of the Martin report. Carbaryl is found in these tables under parameter 82680.

Out of 145 samples taken as ground water field blanks, carbaryl was not detected in any of the samples indicating a lack of false positives. Out of 171 samples taken as surface water field blanks, carbaryl was reported in two samples (1.2% false positives) at reported concentrations of 0.009 and 0.012 μg/L.

A summary of the results for the field matrix spikes and the lab control spikes is presented in Table 6 Mean recovery for the 306 field matrix spikes was 115% of the spiking level of 0.1 μg/L with a median recovery of 94.4% and a 90th percentile recovery of 200%. This indicates the potential for the method to over-estimate the concentration of carbaryl present in the water samples and is consistent with the initial data reported for the reagent water samples by Zaugg *et al*. (1995). Mean recovery for the 1000 lab control spikes was 99.6% of the spiking level of 0.1 μg/L with a median recovery of 93% and a 90th percentile recovery of 185%. These data suggest an adequate level of detection of carbaryl in QC samples that were analyzed as part of the same process used in the NAWQA survey of pesticides in surface and ground water.

Table 6. Percent Recoveries of Carbaryl Detected by the NAWQA GC/MS Method in Laboratory Control Spikes and Field Matrix Spikes at a Spiking level of 0.1 μg/L

Sample Type	Number of Samples	10^{th} Percentile Recovery (%)	Median Recovery (%)	Mean Recovery (%)	90^{th} Percentile Recovery (%)	Maximum Recovery (%)
Field Matrix Spike	306	40	94.4	115.0	199.9	456
Laboratory Control Spike	1000	20	93.0	99.6	185.1	329

The following disclaimer was taken verbatim from the provisional report by Martin (1999) and pertains to the data provided above on the recovery of carbaryl in the field matrix spike samples.

> *"The field matrix-spike data have not been reviewed thoroughly, are provisional, and are subject to change. Further review of the field-spike data is expected to identify spikes that have extremely high or low recoveries because the spikes either were improperly collected or incorrectly documented in the NAWQA QC data base. The expected result of further review is a data set of field matrix spikes with fewer extreme values than the provisional data set described in this paper; consequently, the provisional data set provides a conservative estimate of the quality of the NAWQA pesticide data. Interpretations of field matrix spike data in this paper are not expected to change greatly as a result of further review of the data, however, the statistics and confidence limits reported in the text and tables will change on further review (especially for pesticides with low numbers of field spikes [less than 50])."*

High-Performance Liquid Chromatography/Photodiode-Array Method

Another analytical method used in the NAWQA program for the analysis of carbaryl in water samples is the LC/PDA method described by Werner, *et al*., 1996. This method was used for the analysis of carbaryl in a limited number of samples as noted above. In this multi-residue method, the analytes are first removed from the water sample by sorption on a Carbopak-B solid phase extraction cartridge and are subsequently eluted from the solid phase, separated by HPLC and quantified by light absorption using a photodiode-array detector. The identity of each analyte is confirmed by the appropriate combination of retention time and light absorption characteristics. The recoveries for carbaryl spiked at different levels into three water samples and analyzed by this method is shown in Table 7 The recoveries ranged from 58% to 84% for the different water and spiking levels. Laboratory control spikes in organic-free water resulted in a mean recovery of 61% over a two-year sampling period. These results indicate reasonable levels of carbaryl recovery from each of the different types of water evaluated for the method.

Table 7. Recovery and Precision for Multiple Determinations of Carbaryl in LC/PDA Method for Carbaryl Spiked in Different Water Samples

Water type	Spike Concentration (µg/L)	Mean Recovery (%)	MDL Calculated
Organic-Free	0.1	82	0.008
Organic-Free	1.0	70	-
Surface[A]	0.1	84	0.016
Surface[A]	1.0	84	-
Ground[B]	0.1	58	0.018
Ground[B]	1.0	64	-
Organic-Free	0.5	61[C]	-

[A] Surface water was collected from the South Platte River at Englewood, Colorado.
[B] Ground water was collected from Jefferson County, Colorado (Arvada Well 14).
[C] National Water Quality Laboratory results produced using 5 operators and 7 instruments over 2 years (about 350 data points).

Summary of Surface Water Data from the California DPR Surface Water Database

In Section 5 pages 34 to 37 EPA has summarized surface water monitoring data from various sources. One source not included in this discussion is the California Surface Water Monitoring Database. The number of analyses and the detections of carbaryl residues reported in the database are summarized in Table 8. Carbaryl was detected at levels above the LOQ in only 5.1% of the 2,690 samples analyzed. The mean concentration of carbaryl in the 140 samples above the LOQ was 0.42 ppb. The highest concentration of carbaryl that was detected was 8.4 ppb.

An analysis of the data in the California Department of Pesticide Regulation's surface water database as of July 15, 2000 was conducted for carbaryl. The following summary of the contents of the database is adapted from information provided by the California DPR. The database contains monitoring results for pesticides in samples taken from California rivers, creeks, urban streams, agricultural drains, the Delta, and urban stormwater runoff. As of July 15, 2000, the database contained the results of 30 studies conducted by federal, state, and local agencies, private industry, and an environmental group. A total of 4,660 samples were taken in 16 counties from January 1991 through March 2000. Each record in the database is the result of one analysis for a pesticide active ingredient or breakdown product. The database contains a total of 92,296 analytical records. Only information on the analytical detection of carbaryl in these water samples is summarized in Table 8 below.

Table 8. Carbaryl Detections Reported in California DPR Surface Water Monitoring Database

Land Use Type	Number of Samples	<=LOQ		>0.003 to 0.01		>0.01 to 0.1 ppb		>0.1 to 1 ppb		>1 ppb	
		No.	%	No.	%	No.	%	No.	%	No.	%
All Samples	2690	2553	94.91	13	0.48	55	2.04	55	2.04	14	0.52

Concentrations of analytical results that are reported below the limit of quantification are reported as a zero in the database concentration field. The LOQs for the different methods used to generate the data contained in the database ranged from 0.003 to 0.5 µg/L, with a majority of the samples analyzed with an LOQ of 0.05 µg/L or less (Table 9) .

Table 9. Limits of Quantification for Carbaryl Analytical Methods Reported in California DPR Surface Water Monitoring Database

LOQ (µg/L)	0.003	0.041	0.044	0.05	0.07	0.1	0.5
Number of Samples Analyzed	267	238	168	1353	92	53	146

2. Ground Water Concentrations

In Section 5 page 34 EPA summarized information on the detection of carbaryl in groundwater from the EPA Pesticides in Groundwater Database, the EPA STORET database and the NAWQA database. Each of the databases shows a pattern of very low levels of carbaryl detection in few groundwater resources. These analyses confirm several statements made by the Agency that carbaryl has limited potential to impact groundwater resources. However, on page 2 of the Memorandum issued June 28, 2001, in conjunction with the EFED RED chapter for carbaryl, EPA is requiring additional information on "Surface and groundwater monitoring in urban and suburban use areas (non-guideline)." Based on the characteristics of carbaryl and the available data demonstrating limited impact of carbaryl on ground water resources, additional studies to evaluate the potential for carbaryl to contaminate groundwater are unnecessary and unwarranted.

Summary of Ground Water Data from the NAWQA Program

In Section 5, pages 33 - 34, EPA has summarized ground water monitoring data available for carbaryl. The database that contains the most extensive evaluation of the impact of the most recent uses of carbaryl on ground water is the NAWQA database. One deficiency of the NAWQA program is that samples are targeted to agricultural and urban areas but not to areas treated with the specific chemical being analyzed. However, given the use patterns of carbaryl, the use of carbaryl has certainly occurred near a number of these wells. Another deficiency is that when residues are found, that while they may be representative of residues in ground water, they may not be representative of residues in ground water used for drinking water due to the location of the sampled wells relative to potable drinking water wells.

EPA cited a 1998 review of the NAWQA database by Kolpin and stated:

> *"Carbaryl was detected at greater than the detection limit (0.003 μg/L) in 1.1 % of groundwater samples from 1034 sites across the U.S. by U.S.G.S. NAQWA (sic) program. The maximum observed concentration was 0.021 μg/L."*

This 1998 analysis has been extended by additional study data collected by the NAWQA program. The additional data continue to show a limited number of low level detections of carbaryl in ground water samples. Table 10 below summarizes a more recent provisional review by Kolpin (2001) of the updated NAWQA database. Not all of the water samples were used to calculate the summary statistics as noted by Kolpin:

> *"To preclude bias in these summary statistics from wells that were sampled more than once, the data set was condensed such that each well had a single pesticide analysis. This generally was the first sample collected. However, subsequent samples were selected if these samples contained more pesticide data (i.e., a larger number of pesticides were analyzed). Wells that were designed to be a part of both a land-use study and a major aquifer survey were used in each summary.*

Because of uncertainties in the source of water and contributing land-use area, springs and drains were excluded from these summaries."

Table 10. Carbaryl Detections Reported in Pesticides in Ground Water Update (Kolpin, 2001)

Site Type	Number of Samples	Carbaryl Detection Frequency (%)				Maximum Estimated Concentration (µg/L)
		All	>=0.01 (µg/L)	>=0.05 (µg/L)	>=0.10 (µg/L)	
Agricultural Land-Use Wells	1244	0.40	0.16	0.0	0.0	0.019
Urban Land-Use Wells	634	2.1	1.3	0.0	0.0	0.031
Major Aquifers	1849	0.59	0.54	0.05	0.05	0.539

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Confidential Business Attachment

APPENDIX 1

Surface Water Monitoring for Residues of Carbaryl in High Use Areas of the United States (Stone Environmental, Inc. Report #99-1005-F) (hard copy provided).

Confidential Business Attachment

APPENDIX 2

Calculation of County Average Carbaryl Use Rates (hard copy provided)